Development and Pharmacokinetic Characterization of Pulmonal and Intravenous Delta-9-Tetrahydrocannabinol (THC) in Humans

MYRTHA NAEF,[1] STEFAN RUSSMANN,[2] STEEN PETERSEN-FELIX,[3] RUDOLF BRENNEISEN[1]

[1]Department of Clinical Research, University of Bern, Murtenstrasse 35, CH-3010 Bern, Switzerland

[2]Department of Clinical Pharmacology, University of Bern, CH-3010 Bern, Switzerland

[3]Department of Anaesthesiology, University Hospital of Bern, CH-3010 Bern, Switzerland

Received 21 August 2003; revised 8 December 2003; accepted 11 December 2003

ABSTRACT: The aim of the present study was to develop a physiologically compatible inhalation solution of delta-9-tetrahydrocannabinol (THC), and to compare the pharmacokinetic and analgesic properties of pulmonal THC versus pulmonal placebo and intravenous (iv) THC, respectively. Eight healthy volunteers were included in this randomized, double-blind, crossover study. The aqueous THC formulations were prepared by using a solubilization technique. iv THC (0.053 mg/kg body weight), pulmonal THC (0.053 mg/kg), or a placebo inhalation solution was administered as single dose. At defined time points, blood samples were collected, and somatic and psychotropic side effects as well as vital functions monitored. An ice water immersion test was performed to measure analgesia. Using a pressure-driven nebulizer, the pulmonal administration of the THC liquid aerosol resulted in high THC peak plasma levels within minutes. The bioavailability of the pulmonal THC was $28.7 \pm 8.2\%$ (mean $\pm$ SEM). The side effects observed after pulmonal THC were coughing and slight irritation of the upper respiratory tract, very mild psychotropic symptoms, and headache. The side effects after iv THC were much more prominent. Neither pulmonal nor iv THC significantly reduced experimentally induced pain. J Pharm Sci 93:1176–1184, 2004

Keywords: delta-9-tetrahydrocannabinol; pulmonary aerosol; injection; pharmacokinetics; analgesia

INTRODUCTION

Numerous indications for cannabis preparations and delta-9-tetrahydrocannabinol (THC) have been postulated, with marked differences in the available supporting data. For applications such as nausea and vomiting associated with cancer chemotherapy, anorexia, and cachexia in HIV/AIDS, and spasticity in multiple sclerosis and spinal cord injury, there is strong evidence for medical benefits.[1–4] Relatively well-confirmed effects were described related to painful conditions, especially neurogenic pain, movement disorders, asthma, and glaucoma.[1] In folk medicine, cannabis is widely used to relieve pain of different origins, such as back pain, headache, and migraine.[5] Few human trials have been conducted so far and the outcomes were equivocal.[6] Fifteen to twenty milligrams of oral THC reduced cancer pain significantly, with 20 mg of THC corresponding to 120 mg of oral codeine.[7,8] Intravenous (iv) THC did not affect pain tolerance in dental surgical pain.[9] Analgesia could not be

Correspondence to: Rudolf Brenneisen (Telephone: 41-31-632-87-14; Fax:41-31-632-87-21;
E-mail: brenneisen@dkf5.unibe.ch)

Journal of Pharmaceutical Sciences, Vol. 93, 1176–1184 (2004)

confirmed in a previous pain study with healthy subjects using oral THC (dronabinol, Marinol®) and experimental pain models.[10] Extensive first-pass metabolism by the liver was observed leading to early and high THC metabolite plasma levels. Additionally, the THC plasma peak concentrations showed a high interindividual variability between 30 and 120 min.[10] The bioavailability of orally administered THC is known to be low (6–20%) and to depend on the vehicle and co-ingested food.[11] The peak plasma levels, occurring at 1–5 h after administration, show a strong, also vehicle- and food-dependent variability.[11] After eating cannabis cookies, the bioavailability of THC was 6%,[12] whereas when using THC dissolved in sesame oil in soft gelatin capsules, it was 11 (women) to 19% (men).[13]

These factors make it very difficult to dose oral THC. There is a need for alternative application forms with better pharmacokinetic properties. Ohlsson et al.[12] studied the pharmacokinetic behavior of THC and its clinical effects after iv administration, oral ingestion of cannabis cookies, and smoking cannabis cigarettes. Plasma levels after smoking and iv injection were similar, but low and irregular after ingestion. Peak plasma levels after smoking occurred rapidly and the bioavailability was found to be much higher (18–50%) than after oral (6–20%) administration.[11,12] For a rapid onset of action, the United States Institute of Medicine recommended the development of reliable, and safe THC delivery systems for clinical trials with cannabinoid drugs for symptom management.[14] To the best of our knowledge, there are neither pharmacokinetic data of pulmonally administered THC in humans, except for smoked cannabis, nor data from cannabis-naïve subjects. Therefore, the aim of the present study was to develop and validate *in vitro* and *in vivo* a physiologically tolerable inhalation solution that could be administered with a commercially available nebulizer. In addition, this new application form should be easy to handle, lead to a higher bioavailability as well as early peak plasma levels of THC, and consequently show a rapid onset of action.

EXPERIMENTAL

Materials

The clinical test compound THC (dronabinol) was supplied by THC Pharm GmbH (Frankfurt am Main, Germany). Cremophor® RH 40 was provided from BASF AG (Ludwigshafen, Germany); all other chemicals were of pharmaceutical quality obtained by the pharmacy of the University Hospital of Bern. THC and THC-d_3 used for plasma analysis were obtained from Lipomed (Arlesheim, Switzerland), and (±)-11-hydroxy-Δ^9-THC (11-OH-THC), (±)-11-hydroxy-Δ^9-THC-d_3 (11-OH-THC-d_3), (±)-11-nor-9-carboxy-Δ^9-THC (11-COOH-THC), and (±)-11-nor-9-carboxy-Δ^9-THC-d_3 (11-COOH-THC-d_3) were from Radian (Austin, TX). All solvents were of high-performance liquid chromatography (HPLC) grade and purchased either from Merck (Basel, Switzerland) or Fluka Chemie (Buchs, Switzerland). Bacterial β-glucuronidase (*Escherichia coli*, type IX-A) and *N*,*O*-bis(trimethylsilyl) trifluoracetamide (BSTFA) containing 1% trimethylsilyl chloride (TMCS) were obtained from Sigma-Aldrich (Buchs, Switzerland) and Fluka Chemie, respectively. The solid phase extraction columns (Bakerbond SPE octadecyl cartridges) were purchased from Stehelin (Basel, Switzerland). Roche OnTrak TesTstiks (Roche Diagnostics, Rotkreuz, Switzerland) with a cut-off of 50 ng/mL were used for urine cannabis testing.

Subjects and Study Design

Eight healthy, cannabis-naïve, nonsmoking volunteers (four women, aged 26–35 years, body weight 60 ± 8 kg; four men, 27–50 years, 80 ± 5 kg) were accepted for this randomized, placebo-controlled, double-blind, crossover study which was performed at the Clinical Investigation Unit of the University Hospital of Bern. The subjects were informed about the risks of the study, gave their written informed consent, and were paid for participating. Exclusion criteria were past or existing drug abuse (including alcohol and prescription drugs; cannabis urine test before each session), pregnancy (urine test before first session), positive past history of any psychiatric disorders, and lung diseases. Each subject had to pass lung function tests including vital capacity and forced expiratory volume in 1 s. The subjects were not allowed to take analgesics, alcohol, and caffeinated beverages 48 h before and during the study and were asked to refrain from driving up to 24 h after the end of the study. The study was approved by the Regional Ethics Committee, the Swiss Agency for Therapeutic Products (Swissmedic), and the Swiss Federal Office for Public Health. In the first and second session, each

subject received randomly and double-blinded either the THC (0.053 mg/kg body weight) or the placebo inhalation aerosol. In the third session, THC was administered iv (0.053 mg/kg body weight) over a time period of 2 min. The between-session washout phases were at least 7 days. To familiarize the subjects with the pain test and visual analog scales (VAS), each session began with a training phase, during which the subjects performed a pain test and a 5-min inhalation training with the placebo aerosol. This was followed by recording the baseline of vital functions, side effect scores (VAS), and pain test. After administration of the THC and placebo preparations, vital functions and side effects were recorded and ice water pain determined at 20, 40, 60, 120, 240, and 480 min. Blood (5 mL per time point, corresponding to 45 mL per session, and 135 mL per study) was collected in all three sessions through a peripheral venous catheter from a forearm vein at baseline, 5, 10, 20, 40, 60, 120, 240, and 480 min after administration of the test medications. The heparinized blood samples were centrifuged and the plasma instantly deep-frozen and stored at −20°C until analysis.

Preparation and Validation of the Test Medications

The THC inhalation solution consisted of 0.3% (w/v) of THC, 5.0% (w/v) Cremophor® RH 40, 1.0% (v/v) benzyl alcohol, 0.05% (w/v) sodium ascorbate, and 84.2 mM sodium phosphate buffer (pH 7.4). THC and Cremophor® RH 40 were heated in a water bath at 63°C for 10 min. Two-third of the phosphate buffer, also heated at 63°C, was then incorporated in the mixture by shaking. After cooling to room temperature, benzyl alcohol, sodium ascorbate, and the remaining phosphate buffer were added to the mixture. The clear, yellowish solution was then sonicated for 30 s and finally filtrated through a 0.22-μm filter under aseptic conditions. The placebo inhalation solution was prepared like the THC solution. The THC content and the stability of THC in the inhalation solution, stored at 4°C and protected from light, was controlled by HPLC with diode array detection (HPLC-DAD). The THC content had to be within a range of ±5% of the initial value. Osmolality, viscosity, pH, and sterility were measured according to the standards of the European Pharmacopeia.[15] For the *in vitro* validation of the nebulizer system and the liquid aerosol, the pressure-driven PARI® Master apparatus (Labhardt, Basel, Switzerland) was connected to the tubing followed by the interrupter and the PARI® LC-Plus nebulizer equipped with an inspiratory valve. The nebulizer itself was connected to a PARI® filter set containing a filter pad collecting the aerosol. The filter set was then connected to a 3-L calibration hand pump (3-L Calibrated Syringe; Sensor Medics Corporation, Yorba Linda, CA). Samples of 2 and 3 mL ($n = 3$ each) were nebulized. The inhalation was simulated manually with the hand pump (velocity 1 pull/10 s). The aerosol absorbed on the filter pad was then extracted with ethanol, lyophilized, redissolved in ethanol, and analyzed by HPLC-DAD. The particle size distribution was determined by using a Malvern Mastersizer X equipped with a 100-mm lens and Malvern Software, Malvern, UK (using the algorithm for volume distribution, polydisperse aerosol, and the 2QAA-model representing water in air). To minimize light scattering, the room was darkened during the measurements. Temperature and humidity were kept constantly at 23°C and 40%, respectively. For the sample analysis, the inhalation solution was nebulized continuously into the laser beam and continuously removed by a vacuum cleaner. The obscuration was held on a value of approximately 10–30%. The particle size distribution was measured in the vehicle ($n = 10$) and in the THC liquid aerosol ($n = 5$). The injection solution consisted of 0.1% (w/v) of THC, 1.5% (w/v) Tween® 80, 5.0% (v/v) ethanol absolute, 0.1% (w/v) sodium ascorbate, and sodium chloride solution (0.9%).[16] Sodium ascorbate was added to prevent the oxidation of THC to cannabinol. THC was dissolved in ethanol and Tween® 80, then added to the sodium ascorbate dissolved in 1 mL of the sodium chloride solution. The remaining sodium chloride solution was finally added to the mixture. The clear, yellowish solution was then sonicated for 30 s and filtrated through a 0.22-μm filter under aseptic conditions.

Inhalation Procedure

The pressure-driven inhalation device PARI® Master and the PARI® LC-plus nebulizer with interrupter were used. The subjects were instructed to inhale deeply with a breath frequency of 1 breath per 10 s waiting for 3–5 s before expiration. The subjects were instructed to continue until all the inhalation solution had been inhaled. Inhalation time and any residue left in the nebulizer compartment were measured.

Pain Test

A standardized 2-min ice water test (ice cold immersion test) was used as model for acute pain.[17–19] The right hand was immersed in ice-saturated water ($1.6 \pm 0.04^{\circ}C$) and if pain was considered as intolerable before 2 min had elapsed, the subject could withdraw the hand. Perceived pain intensity was rated continuously with an electronically controlled VAS system and recorded on a computer. Peak pain, area under the pain intensity-time curve, and mean pain were determined. If the hand was withdrawn before the end of 2 min, pain intensity was considered to be maximal until the end of the 2-min period (for calculation of the area under the curve).

Monitoring of Side Effects

A VAS was used to asses psychological and somatic side effects, such as sedation, euphoria, anxiety, nausea, vertigo, headache, irritation of airways, etc. The volunteers were instructed to report how they felt at the moment of answering the VAS questionnaire. On the 10-cm VAS scale, 0 cm (0%) represented "not at all," 10 cm (100%) represented "very strong." Hemoglobin oxygen saturation (pulse oximetry), blood pressure, and heart rate were recorded by using an HP 78352C patient monitoring system from Hewlett Packard.

Statistical Analysis

The Wilcoxon matched-pairs signed-rank test for nonparametric data was used for comparison of the side effects in the pulmonary application sessions. $p < 0.05$ was considered as significant. No statistical comparison was made with the results from the iv session because this THC application was not blinded. Analyses were performed in STATA, version 8.1 for MacOS X (STATA Corp., College Station, TX).

Analysis of Plasma Samples

Plasma concentrations of THC and its metabolites 11-OH-THC and 11-COOH-THC were determined by gas chromatography/mass spectrometry. Extraction of the 0.5-mL plasma aliquots was performed automatically by using an ASPEC XL (Automatic Sample Preparation with Extraction Columns) system equipped with a Dilutor 402 (Gilson, Villiers Le Bel, France) and applying the method of Moeller et al.[20] Hydrolyzation, derivatization, and gas chromatography/mass spectrometry analysis were performed according to the method of Feng et al.[21] The method was linear in the following calibrated ranges: from 0.4 to 20 ng/mL for THC in the lower concentration levels, from 20 to 300 ng/mL for THC in the higher concentration levels, and from 0.4 to 100 ng/mL for the two metabolites 11-OH-THC and 11-COOH-THC. Samples exceeding the linearity range were diluted with blank plasma, re-extracted, and again analyzed. The limit of quantification for THC and its metabolites was 0.4 ng/mL plasma.

Pharmacokinetic Calculations

Plasma concentrations versus time were used to calculate pharmacokinetic parameters, including plasma peak concentrations (C_{max}), time to reach peak plasma concentrations (t_{max}), and area under the concentration-time curve (AUC). Based on a noncompartmental model, all pharmacokinetic parameters were assessed by use of standard calculation procedures performed by the TopFit (version 2.0) computer software.[22] AUC from time 0 to infinity ($AUC_{0-\infty}$) or the time corresponding to the last measurable concentration (AUC_{0-x}) was calculated by numeric integration using the linear trapezoidal rule. Values for C_0 (extrapolated) were determined by linear regression of the logarithmically transformed concentration values back to the time point 0.

RESULTS

The results of the quality assurance of the test medications, which allowed their clinical use, are listed in Table 1. Figures 1 and 2 show the plasma profiles of THC and the two metabolites 11-OH-THC and 11-COOH-THC after pulmonal and iv administration, respectively. None of the baseline samples showed measurable concentrations of THC or THC metabolites. The mean plasma level of pulmonal THC after 10 min was 18.7 ± 7.4 ng/mL (mean $\pm$ SEM) with a mean duration of the inhalation procedure of 23 ± 3 min. The peak plasma levels of 18.9 ± 5.0 ng/mL were measured at 20 min (Fig. 1). Then, the plasma concentrations decreased rapidly. Peak plasma levels of the two main metabolites 11-OH-THC and 11-COOH-THC were 1.4 ± 0.3 ng/mL occurring at 40 min and 10.0 ± 2.9 ng/mL at 120 min, respectively. The plasma levels 5 min after the iv injection of

Table 1. *In Vitro* Validation and Quality Assurance of the Test Medications

Test	Inhalation Solution	Injection Solution
Stability	3 months	3 weeks
Osmolality	550 mOsm/kg	321 mOsm/kg
Viscosity	1.478 mPas	Not determined
pH value	7.40	7.40
Output rate	$63.5 \pm 4.4\%$ (mean $\pm$ SD)	Not determined
Particle size distribution	3.8 ± 0.32 μm (median $\pm$ SD)	Not determined
Sterility	Not determined	Passed

THC (0.053 mg/kg body weight) ranged from 81.6 to 640.6 ng/mL (271.5 ± 61.1 ng/mL; Fig. 2). After that, the plasma levels decreased rapidly. Peak plasma levels of 11-OH-THC and 11-COOH-THC were 9.1 ± 0.8 ng/mL occurring at 5 or 10 and 36.7 ± 3.8 ng/mL occurring at 60 min, respectively. The ratio of the AUC_{0-480} of THC to the AUC_{0-480} of its psychoactive metabolite 11-OH-THC was 4.4 to 1 and 6.6 to 1 after pulmonal and iv THC, respectively. Tables 2 and 3 summarize the pharmacokinetic parameters for pulmonal and iv THC. The approximate half-lives for iv and pulmonal THC were 73 and 46 min, respectively.

The observed psychological and somatic side effects are depicted in Table 4 and Figure 3. After pulmonal THC, the symptoms irritation of the throat and upper respiratory tract, and coughing were highly significant compared with placebo. These side effects were reversible within 30 min of finishing inhalation. In contrast to iv THC, the psychotropic effects after pulmonal THC were usually very mild. A significant difference versus pulmonal placebo was observed for pulmonal THC concerning euphoria, confusion and disorientation, and change of inner perception. Blood pressure was not changed by THC, whereas both pulmonal and iv THC increased heart rate significantly as compared with placebo (data not shown).

As after oral THC,[10] pulmonal THC produced hyperalgesia in the ice water pain test, an effect which was significant versus pulmonal placebo only after 20 min (Table 5).

DISCUSSION

It was possible to develop an aqueous inhalation solution of the very hydrophobic THC. The output rate of the nebulizer device was sufficient to deliver the required dose of THC within an inhalation time of 20–25 min. The resulting droplet size should allow the aerosolized THC to reach the lower compartments of the lung, thus enabling a high absorption rate. The quality assurance of the pulmonal and iv formulation showed good stability and physiological compatibility. The pulmonal application of nebulized THC, therefore, seems to be a promising mode for the clinical use of THC. The pulmonal bioavailability of $28.5 \pm 23.1\%$ (0.4–60.6%) was higher than after oral administration, where the bioavailability was found to be 5–20%.[11–13] Some volunteers even

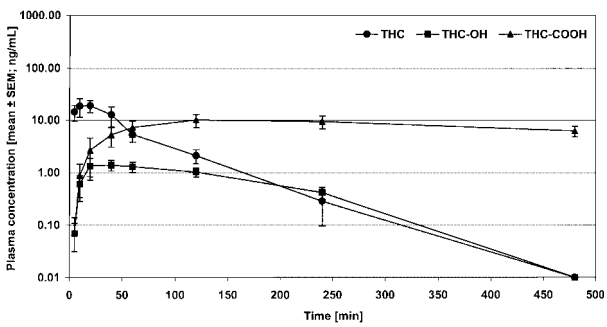

Figure 1. Plasma concentrations (mean $\pm$ SEM; $n = 8$) of THC and its main metabolites 11-OH-THC and 11-COOH-THC after pulmonal THC.

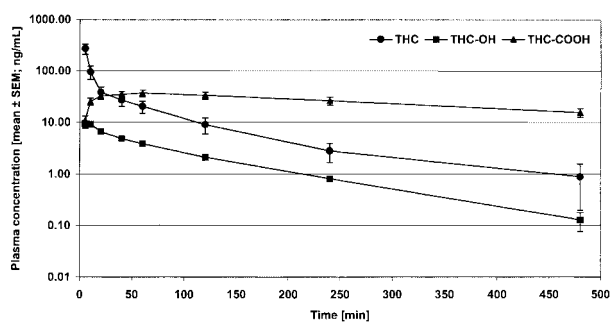

Figure 2. Plasma concentrations (mean $\pm$ SEM; $n = 8$) of THC and its main metabolites 11-OH-THC and 11-COOH-THC after iv THC.

Table 2. Pharmacokinetic Parameters of Pulmonal Versus iv THC

Subject		Pulmonal THC				iv THC	
No.	Gender	Dose (mg)	$AUC_{0-\infty}$ ($ng \cdot min \cdot mL^{-1}$)	Bioavailability F (%)	Elimination Rate Constant λ_z ($\cdot 10^{-2}$)	Dose (mg)	$AUC_{0-\infty}$ ($ng \cdot min \cdot mL^{-1}$)
1	F	3.71	2528	38.8	1.600	3.30	5792
2	M	2.98	694	28.5	1.500	4.20	3437
3	M	4.08	2607	59.4	1.090	4.24	4559
4	M	4.56	1257	21.4	1.710	4.53	5827
5	F	2.34	68	0.4	3.890	2.40	20103
6	F	2.97	528	15.3	1.570	2.92	3406
7	F	3.29	367	3.7	0.823	3.50	10506
8	M	4.03	1581	60.5	0.225	4.00	2592
Mean ± SD			1203 ± 969	28.5 ± 23.1	1.550 ± 1.070		7028 ± 5829

F, female; M, male.

showed a bioavailability of >40%. A study comparing the bioavailability of oral and pulmonal THC in individual volunteers would lead to more conclusive results. Most of the subjects reached plasma levels comparable to those of iv THC at 10 and 20 min. Peak plasma levels of THC were observed before the end of the inhalation procedure.

Regarding the plasma concentrations of the THC metabolites 11-OH-THC and 11-COOH-THC, similar patterns for pulmonal and iv THC were observed. The THC to 11-OH-THC-ratios found in the present study for iv THC, and in an earlier study[10] for oral THC, confirm the findings reported by Wall et al.[13] for iv THC. The significantly lower formation of the psychoactive 11-OH-THC after pulmonal THC, due to the absence of first-pass metabolism, results in remarkably less intensive psychotropic side effects compared with oral THC. This is an important fact regarding the development of future THC application forms.

The plasma concentration-time plot of the iv administration showed first a distribution phase with a very rapid decrease of the THC plasma levels followed by the elimination phase with a much longer terminal plasma elimination half-life. This pattern is compatible with two-compartment elimination kinetics described previously by Wall et al.[13] and Huestis.[11]

The placebo aerosol was very well tolerated indicating a good tolerability of the vehicle with the adjuvants used for solubilization and stabilization of the formulation. Nevertheless, irritation of the airways and coughing after pulmonal THC was observed for all subjects, meaning that THC itself caused these adverse effects ($p = 0.01$). Coughing

Table 3. Pharmacokinetic Parameters of iv THC

Subject		iv THC		
No.	Gender	Distribution Volume V_{ss}/kg Body Weight (Steady State) (L/kg)	Clearance CL/kg Body Weight ($mL/min \cdot kg$)	Elimination Rate Constant λ_z ($\cdot 10^{-2}$)
1	F	0.847	8.14	0.578
2	M	0.598	15.44	1.370
3	M	0.403	12.08	1.400
4	M	0.300	9.03	1.500
5	F	0.324	3.41	0.566
6	F	0.668	15.30	1.320
7	F	0.431	5.37	0.813
8	M	1.120	20.26	1.280
Mean ± SD		0.586 ± 0.285	11.13 ± 5.69	1.100 ± 0.390

F, female; M, male.

Table 4. Psychological and Somatic Side Effects (VAS) after Pulmonal THC and Placebo and iv THC

	Median of Maximum Values on VAS			
Symptom on VAS	iv THC	Pulmonal THC	Pulmonal Placebo	p Value[a] (Pulmonal THC vs. Pulmonal Placebo)
Sleepiness	89	64	22.5	0.12
Euphoria	62.5	20.5	0	0.02
Irritation	25	2	0	0.05
Anxiety	26.5	0	0	0.45
Tenseness and aggressiveness	18.5	1	0	0.45
Confusion and disorientation	80	2	0	0.03
Change of inner perception	85.5	9.5	0	0.03
Change of outer perception	72.5	0	0	0.09
Hallucinations	35	0	0	0.16
Strange thoughts, ideas, moods	34	0	0	0.32
Nausea	25	8	0	0.05
Headache	43	16.5	0	0.11
Difficulties in breathing	27.5	8.5	0	0.03
Irritation of the throat, coughing	0	75	2	0.01
Irritation of the upper respiratory tract	1.5	79.5	0	0.01
Heart problems (tachycardia)	34.5	0	0	0.16
Digestive problems	7.5	0	0	0.93
Dry mouth	100	3	3	0.48
Vertigo	76	30.5	0	0.03

[a]Wilcoxon matched-pairs signed-rank test.

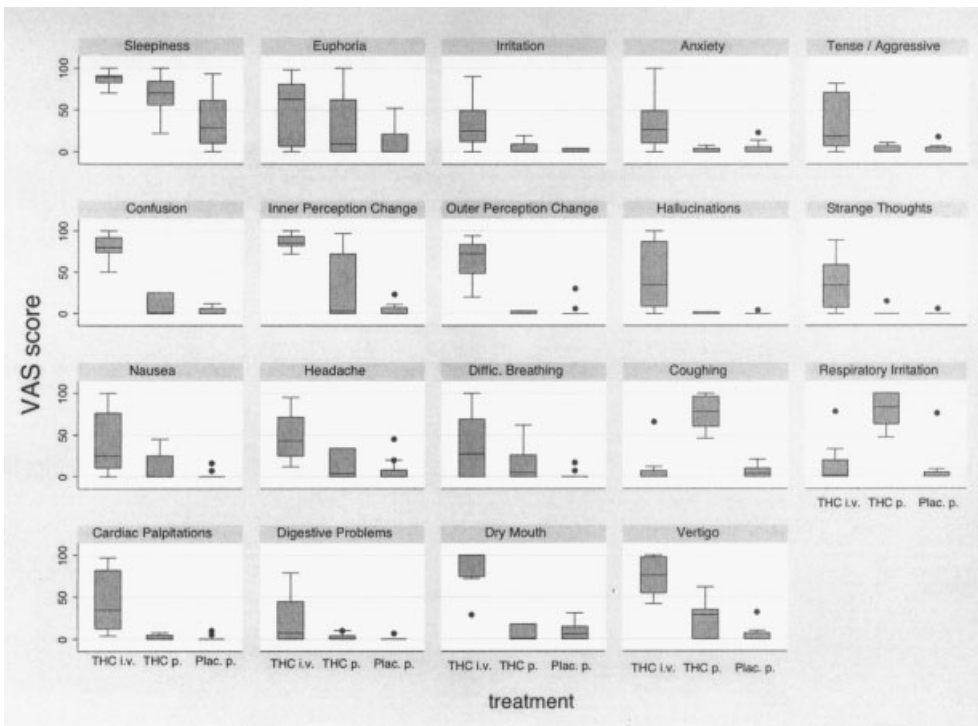

Figure 3. Psychological and somatic side effects after pulmonal and iv THC and pulmonal placebo. Box and whisker plots according to VAS showing median, interquartile range, lower and upper adjacent values, and outside values.

Table 5. Pain Tolerance in the Ice Cold Immersion Test after Pulmonal THC and Placebo

Time (min)	Median AUC Pain Test (Difference from Baseline)		p Value[a] (Pulmonal THC vs. Pulmonal Placebo)
	Pulmonal THC	Pulmonal Placebo	
20	127	26	0.03
40	54	34	0.21
60	129	80	0.53
120	170	62	0.12
240	160	127	0.89
480	235	99	0.67

[a]Wilcoxon matched-pairs signed-rank test.

impaired the inhalation procedure, and therefore, most likely also the interindividually most variable bioavailability, which would probably be higher with a less irritating formulation of THC. The irritations were reversible within a short time after the end of inhalation indicating no lasting damage to the mucosa. This particular effect of THC was also demonstrated by Tashkin et al.[23] Because the micellar formulation used in this study did not prevent mucosal irritation, other techniques should be tested, for example the use of liposomes or microencapsulation. A higher mean C_{max} and very rapid increase in concentration in the central nervous system were responsible for the more pronounced adverse effects of iv THC, which were mainly of a psychotropic nature. THC did not reduce pain in the ice water test after pulmonal administration. This confirms the ice water test results obtained in our previous study with oral THC. As postulated before,[10] this indicates that the low oral bioavailability of THC is not responsible for the lack of analgesia. It is assumed that the ice water test is not the right model to determine an analgesic effect of THC.

In conclusion, the pulmonal administration of a liquid THC aerosol leads to rapid and high plasma levels of THC, with a metabolic pattern similar to that of iv THC. Although the bioavailability was much higher than after oral THC, no significant analgesic effect was measured with an acute pain test. Because appropriate experimental chronic pain models are currently not available, the analgesic effect of pulmonal THC should be further tested in pain patients. In addition, other solubilization techniques should be evaluated to improve the physiological tolerability of pulmonal THC aerosols.

ACKNOWLEDGMENTS

The authors thank THC Pharm (Frankfurt/M., Germany) for the supply of THC, the Swiss Federal Office for Public Health for sponsoring the study (grant 02.000330/2.24.02-150), and the staff of the Clinical Investigation Unit for assistance.

REFERENCES

1. Grotenhermen F. 2002. Review of therapeutic effects. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids: Pharmacology, toxicology, and therapeutic potential. New York: The Haworth Press, pp 129–142.
2. Baker D, Pryce G, Giovannoni G, Thompson AJ. 2003. The therapeutic potential of cannabis. Lancet Neurol 2:291–298.
3. Croxford JL. 2003. Therapeutic potential of cannabinoids in CNS disease. CNS Drugs 17:179–202.
4. Smith PF. 2002. Cannabinoids in the treatment of pain and spasticity in multiple sclerosis. Curr Opin Investig Drugs 3:859–864.
5. Ogborne AC, Smart RG, Weber T, Birchmore-Timney C. 2000. Who is using cannabis as medicine and why: An exploratory study. J Psychoactive Drugs 32:435–443.
6. Campbell FA, Tramèr MR, Carroll D, Reynolds DJM, Moore RA, McQuay HJ. 2001. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. Br Med J 323:13–16.
7. Noyes RJ, Brunk SF, Baram DA, Canter A. 1975. Analgesic effect of delta-9-tetrahydrocannabinol. J Clin Pharmacol 15:139–143.
8. Noyes RJ, Brunk SF, Baram DA, Canter A. 1975. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther 18:84–89.

9. Raft D, Gregg J, Ghia J, Harris L. 1977. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlates of the analgesic response. Clin Pharmacol Ther 21:26–36.
10. Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. 2003. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC–morphine combination in healthy subjects under experimental pain conditions. Pain 105:79–88.
11. Huestis M. 1999. Pharmacokinetics of THC in inhaled and oral preparations. In: Nahas GG, Harvey D, Agurell S, editors. Marihuana and medicine. Totowa, NJ: Humana Press, pp 105–116.
12. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther 28:409–416.
13. Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. 1983. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther 34:352–363.
14. Joy JE, Watson SJ, Benson JA. 1999. Marijuana and medicine, assessing the science base. Washington DC: National Academic Press, pp 1–14.
15. European Pharmacopeia, 4th ed., Vol. 1. 2002. Stuttgart, Germany: Deutscher Apotheker Verlag.
16. Olsen JL, Makhani M, Davis KH, Wall ME. 1973. Preparation of 9-tetrahydrocannabinol for intravenous injection. J Pharm Pharmacol 25:244.
17. Jones SF, McQuay HJ, Moore RA, Hand CW. 1988. Morphine and ibuprofen compared using the cold pressor test. Pain 34:117–122.
18. Sindrup SH, Poulsen L, Brosen K, Arendt-Nielsen L, Gram LF. 1993. Are poor metabolisers of sparteine/debrisoquine less pain tolerant than extensive metabolisers? Pain 53:335–339.
19. Petersen-Felix S, Arendt-Nielsen L, Bak P, Bjerring P, Breivik H, Svensson P, Zbinden AM. 1994. Ondansetron does not inhibit the analgesic effect of alfentanil. Br J Anaesth 73:326–330.
20. Moeller MR, Doerr G, Warth S. 1992. Simultaneous quantitation of delta-9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) in serum by GC/MS using deuterated internal standards and its application to a smoking study and forensic cases. J Forensic Sci 37:969–983.
21. Feng S, ElSohly MA, Salamone S, Salem MY. 2000. Simultaneous analysis of delta-9-THC and its major metabolites in urine, plasma, and meconium by GC-MS using an immunoaffinity extraction procedure. J Anal Toxicol 24:395–402.
22. Heinzel G, Woloszczak R, Thomann P. 1993. Topfit: Pharmacokinetic and pharmacodynamic data analysis system for the PC. Stuttgart, Germany: G. Fischer.
23. Tashkin DP, Reiss S, Shapiro BJ, Calvarese B, Olsen JL, Lodge JW. 1977. Bronchial effects of aerosolized delta-9-tetrahydrocannabinol in healthy and asthmatic subjects. Am Rev Respir Dis 115:57–65.