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Pain response to cannabidiol in opioid-induced hyperalgesia, acute nociceptive pain, and allodynia using a model mimicking acute pain in healthy adults in a randomized trial (CANAB II)

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Abstract

Opioids in general and remifentanil in particular can induce hyperalgesia. Preclinical data suggest that cannabidiol might have the capacity to reduce opioid-induced hyperalgesia (OIH). Thus, we investigated the effect of oral cannabidiol on OIH in healthy volunteers using an established pain model. Twenty-four healthy participants were included in this randomized, double-blinded, crossover study and received either a 1600-mg single-dose oral cannabidiol or placebo. Hyperalgesia, allodynia, and pain were induced by intracutaneous electrical stimulation. To provoke OIH, participants recieved an infusion of 0.1 μg/kg/min remifentanil over a time frame of 30 minutes, starting 100 minutes after oral cannabidiol ingestion. The primary outcome was the area of hyperalgesia (in square centimetres) up to 60 minutes after remifentanil administration. The area of allodynia (in square centimetres) and pain (numeric rating scale) were also assessed.

Cannabidiol had no significant effect on hyperalgesia, allodynia, or pain at any time point of measurement compared with placebo. The area of hyperalgesia after remifentanil administration significantly increased compared with baseline (17.0 cm^2 [8.1-28.7] vs 25.3 cm^2 [15.1-39.6]; $P = 0.013$). Mean cannabidiol blood levels were 4.1 ± 3.0 μg/L (mean ± SD) at 130 minutes after ingestion and were 8.2 μg/L ± 6.9 μg/L (mean ± SD) at 200 minutes. Cannabidiol was well tolerated. We conclude that a high single-oral dose of 1600-mg cannabidiol is not effective in reducing OIH. Before excluding an effect of cannabidiol on OIH, research should focus on drug formulations enabling higher cannabidiol concentrations.

Keywords: Cannabidiol, Acute pain, Hyperalgesia, Allodynia, Opioid-induced hyperalgesia, Remifentanil

1. Introduction

Since the synthesis of fentanyl by Paul Janssen in 1960, it has become possible to administer very high doses of opioids.[22] Since then, modern anaesthesia typically involves a potent opioid for perioperative analgesia.[12,19,62] However, despite sparse data of clinical prevalence,[41,71] opioid-induced hyperalgesia (OIH) is a well-described phenomenon.[1,20,24,32] High doses of intraoperative opioids[11] lead to increased postoperative pain[21] and opioid requirements.[24] Despite the named problems, the perioperative use of opioids is a cornerstone therapy.[61] This is particularly the case for high-risk patients with contraindications for alternative potent treatment options of multimodal analgesia.[12,19,66] Adjunct therapeutics with the potential to reduce opioid requirements or OIH could offer a solution to this problem.

After decades of low research activity,[46] findings regarding the pain modulation properties of the endocannabinoid system[30,40] have brought cannabinoids back into focus. As a nonpsychoactive substance,[4,40] cannabidiol (CBD) would be an attractive option as an opioid adjunction therapy. It has low potential for abuse,[3] has well-tolerated side effects,[68] and is low risk for relevant drug-interactions.[65] The functional actions of CBD especially on analgesia are mostly based on animal data.[16,42,55] The complex interaction on several different levels of the pain signalling pathway[15,18,36,40] makes CBD an interesting compound to be investigated in humans, even the molecular targets in pain processing for analgesic effects are not clearly defined yet.[76]

A recent systematic review and meta-analysis of cannabinoids supports the hypothesis of cannabinoid-induced analgesia,[63] but because of the lack of clinical evidence, the IASP does not yet advocate for the use of CBD for pain relief in humans.[9]

Rodriguez-Munoz et al.[55] demonstrated the ability of CBD to enhance morphine antinociception in mice. They suggested that CBD acts as σ1-receptor antagonist[56] and diminishes the influence of glutamate NMDA receptors.[55] This is an interesting approach because we know that OIH is caused by central sensitization through N-methyl D-aspartate (NMDA) receptors.[2,12] This brings up the question of whether CBD might be

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able to diminish OIH in humans or show synergistic analgesic effects with opioids.[56]

The pain model applied in this study is able to produce and quantify OIH in healthy volunteers.[2,34,35,44] If CBD can reduce OIH, it might be a valuable adjunct for opioid-based anaesthesia and analgesia.

In this randomized, placebo-controlled, double-blinded, crossover study, we examined the effect of 1600-mg orally administered CBD on OIH (in square millimeters) in healthy volunteers in a well-established pain model.[34] We hypothesized that CBD could significantly reduce the area of hyperalgesia during an observation period of 60 minutes after termination of a remifentanil infusion used to induce hyperalgesia. In a previous study of our group, placebo application without deception reduced the area of hyperalgesia about 20%.[57] This was set as the lowest level of expected effect using an active compound. Secondary outcomes included the effect of CBD on pain (numeric rating scale [NRS]) and area of allodynia (in square millimeters).

2. Material and methods

2.1. General study design

The local ethics committee (ID 2019-01217; Ethikkommission Nordwest-und Zentralschweiz, Basel, Switzerland) and the medical approval agency Swissmedic (ID 2020DR2016) approved this study (registered at clinicaltrials.gov [NCT04059978]) before recruitment. The study was conducted in accordance with the Declaration of Helsinki at the University Hospital of Basel, Basel, Switzerland, after obtaining written informed consent from each volunteer.

This study is a prospective, randomized, placebo-controlled, double-blinded, crossover study examining the effect of CBD on OIH, allodynia, and pain. Each volunteer underwent 2 interventions of electrically induced acute pain (**Fig. 1**). Between the first and second intervention, a minimum washout period of 2 weeks was required to avoid habituation effects and to ensure complete CBD clearance. In both interventions, participants received a remifentanil infusion for 30 minutes, 100 minutes after ingestion of the CBD or placebo to induce OIH. The participants received either 1600 mg of oral CBD or placebo after 6 hours of fasting. A syringe pump (Injectomat Agilia, Fresenius Kabi, Bad Homburg, Germany) was used to intravenously administer 0.1 μg/kg/min remifentanil. During the interventions, participants were continuously monitored by pulse oximetry (IntelliVue X2, Philips, Best, the Netherlands) and regularly asked about their well-being to screen for possible side effects. All reported side effects were protocoled at the case report form. Randomization of the study medication order was conducted by random number generator. The pharmacy of the University Hospital of Basel provided the study medication for each participant with a medication ID for the first and second interventions. To prevent accidental interchange, study medication was only provided per experiment of one single participant by the pharmacy. Because of the medication ID, the member of the study team responsible for assessing pain, hyperalgesia, and allodynia and the participant were blinded to the order of the study medication. The experiments were conducted twice a day, starting 08.30 AM respective 1 PM in a separate room in the hospital with access restricted to participants and the study staff only. External interference and noise were kept to a minimal. Participants were positioned in a comfortable lying position with the arm used for measurements abducted at 45°. During sensory testing, the participants were instructed to keep their eyes shut, settings of current generator were not visible for participants. All measurements were performed by the same study investigator to minimize differences in interpersonal evaluation.

Pain, hyperalgesia, and allodynia were assessed every 10 minutes for 100 minutes (**Fig. 2**). A NRS (0, no pain and 10, worst pain imaginable) was used to assess the level of pain. Hyperalgesia was determined using a 256 mN von Frey filament and allodynia using a dry cotton swab to assess the affected area.

2.2 Subjects

Volunteers were recruited through an advertisement on the homepage of the University of Basel, and inclusion occurred on a "first come, first served" basis with a balanced sex distribution (50% male and 50% female volunteers). Inclusion criteria were healthy (American Society of Anesthesiologists Physical Status I-II) adults (18 years and older) with a body mass index of 18.5 to 25 kg/m^2 (**Fig. 1**). Exclusion criteria were frequent consumption of cannabinoids or other intoxicants, and regular intake of medications potentially interfering with pain sensation (analgesics, antihistamines, calcium and potassium channel blockers, antidepressants, corticosteroids). Neuropathy, chronic pain, neuromuscular disease, psychiatric disease, known or suspected kidney or liver disease, pregnancy/lactation, or a known allergy/hypersensitivity to CBD or remifentanil also leads to exclusion. Female participants in childbearing age were tested for pregnancy prior each intervention and received information concerning contraception in the participant information.

The experimental setup, including the assessment of pain (NRS), hyperalgesia, and allodynia, was explained to the volunteers prior to the first intervention, and financial compensation for participation in the study was paid.

2.3 Study medication

The study medications, manufactured by the pharmacy of the University Hospital of Basel, were provided in single-dose brown-glass bottles (8 mL volume) labelled in a blinded manner (for each participant and intervention, 2 bottles with a medication ID for the first and second intervention).

The investigational medical product (IMP) contained 800 mg CBD in 8 mL oily solution per bottle for per os administration. The placebo solution only contained 8 mL oily solution and was matched to the IMP so that it could not be distinguished by either the participant or the assessor. To achieve a dosage of 1600-mg CBD for each intervention, 2 bottles of the IMP or placebo solution were administered.

2.4 Remifentanil

Intravenous remifentanil infusions with a dose of 0.1 μg/kg/min for 30 minutes were used in previous studies investigating the OIH in the same acute pain model.[2,33,35] In the present study, a 2-mg ampoule of lyophilized dry substance was prepared with NaCl 0.9% (0.02 mg/mL concentration), and a syringe driver (Injectomat Agilia, Fresenius Kabi, Bad Homburg, Germany) was used to intravenously administer 0.1 μg/kg/min.

According to Koppert et al.[35] after 30 minutes of infusion calculated plasma levels achieved a steady state with only moderate sedation and a slight decrease in oxygen saturation without further side effects.

2.5 Experimental pain model and assessment

Every volunteer passed through 2 interventions with intradermal electrically induced pain by directly activating C fibers primarily and A-delta fibers to smaller degree.[34] Xanthos et al.[74]

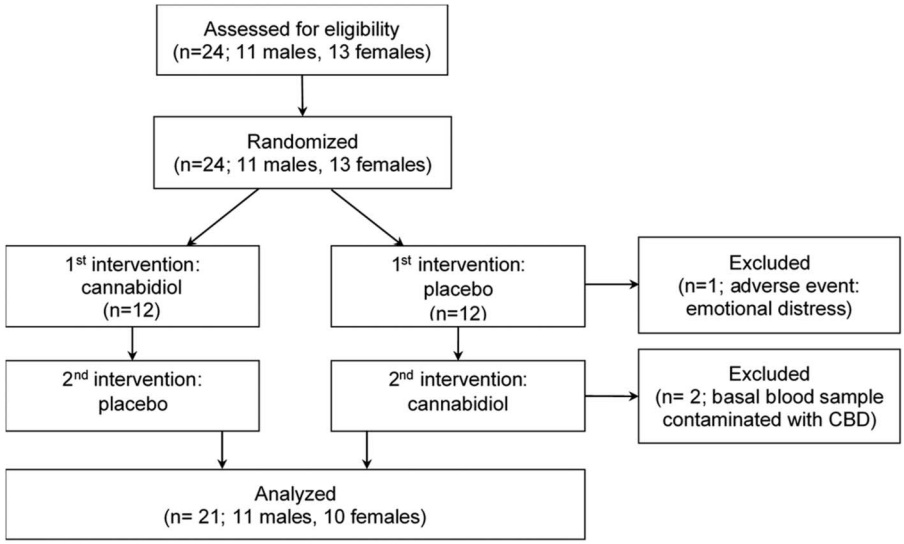

Figure 1. Participant randomization scheme CBD, cannabidiol.

conceptualized the broad activation of the nociceptive system by the applied current as neurogenic neuroinflammation. The model allows the simultaneous assessment of evoked pain and central (spinal) sensitization, as it produces stable secondary hyperalgesia and allodynia over time.[69] Furthermore, it has been a reliable tool to induce and assess OIH during prior studies.[33,35,44] Because of broad activation and reflection of the pain pathway, it does not allow a specific evaluation of the exact mechanisms of an effect.

Two microdialysis catheters with internal stainless steel wires were inserted in parallel into the intradermal, volar surface of the right forearm for a length of approximately 10 mm and separated by 5 mm from each other. The catheters were filled with 0.9% saline, and a continuous flow of 0.2 μL/min was ensured by a syringe pump (CMA 402, CMA Microdialysis AB, Kista, Sweden) to facilitate conduction. The stainless steel wires were attached to a constant current stimulator (Digitimer S7; Digitimer Ltd, Hertfordshire, United Kingdom), and monophasic rectangular electrical pulses of 0.5-millisecond duration were applied with alternating polarity at 2 Hz. The current was titrated to target a pain rating of 6 of 10 on an NRS (0 = no pain, 10 = worst pain imaginable).

To compensate for early pain habituation, adjustments were made during 15 minutes after installation to reach a stable 6 out 10 on the NRS for each intervention. For 100 minutes, volunteers were asked to rate the NRS at every 10-minute interval. Hyperalgesia and allodynia areas were assessed by the investigator accordingly. The volunteer was blinded to the applied milliampere (mA) values. One-hundred minutes after IMP administration, an infusion of 0.1 μg/kg/min remifentanil for 30 minutes was administered to cause OIH. Previous studies showed that shortly after the remifentanil infusion was terminated, hyperalgesia increased and the hyperalgesic area remained significantly enlarged compared with baseline values.[35]

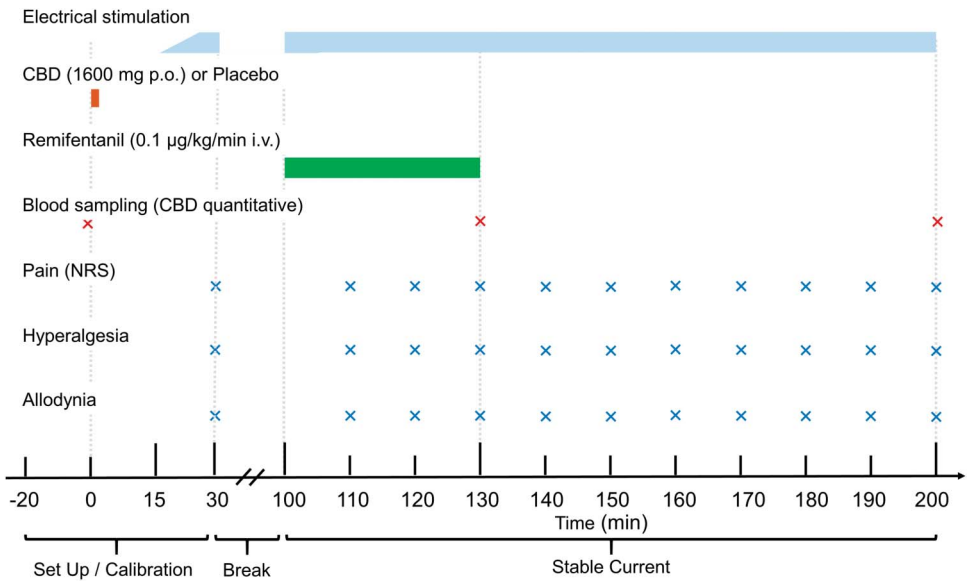

Figure 2. Schematic illustration of experimental setup. CBD, cannabidiol;NRS, numeric rating scale.

Table 1

Baseline characteristics.

Baseline characteristics	
No. of participants	24
Age	25 ± 7
Male	11 (45.8%)
Female	13 (54.1%)
BMI [kg/m^2]	22.0 ± 1.9
Ethnicity	
White European	22 (91.6%)
Asian	1 (4.2%)
Mixed African European	1 (4.2%)

Data shown as median with interquartile range (age) and mean with SD (BMI).
BMI, body mass index.

2.6 End points

The primary end point was the area of hyperalgesia measured from minute 140 to minute 200 after oral application of CBD. This equalized 10 minutes after the termination of a 30-minute remifentanil infusion (**Fig. 2**). Secondary end points were the effect of CBD vs placebo on the NRS and area of allodynia measured during the same period. In addition, whole-blood CBD levels at baseline and at 130 minutes and 200 minutes after oral administration were measured. We also analyzed the effect of remifentanil on pre- and postinfusion assessments.

2.7 Assessment of hyperalgesia and allodynia

The area of pinprick hyperalgesia was determined using a 256 mN von Frey filament, and subsequently, the area of allodynia was determined using a dry cotton swab. Measurements were conducted from a more distant to a more central site along 4 orthogonal lines (distal, proximal, lateral, and medial) drawn onto the skin with tick marks indicating each centimeter. Distal and proximal measurements were begun 12 cm from the site of electrical stimulation, whereas lateral and medial measurements were begun a maximum of 6 cm from the site, depending on the size of the forearm. In both cases, the instrument was moved toward the site of stimulation in 1-cm increments until the subject reported either increased pain sensations from the von Frey filament (hyperalgesia) or an unpleasant, "rougher" sensation from the cotton swab gently stroked on the skin (allodynia). Each direction was at least measured twice per time point to ensure consistent data. To create an area from these linear measurements, we assumed the field to be elliptic. The area was calculated using the formula: π D· d (where D is the vertical diameter and d the horizontal diameter). To not overestimate the impact of the wide axis measurements, a minimum of 1-cm radius was defined.

2.8 Measurement of cannabidiol whole-blood levels

To determine CBD levels in whole blood, blood was drawn from a peripheral catheter placed in the cubital vein of the arm not used for electrical stimulation. Three blood samples (SARSTEDT Monovette 9 mL, custom made potassium fluoride 45 mg/9 mL, reference number: 17,265, Hôpital du Valais, Switzerland) were drawn immediately before, at 130 minutes, and at 200 minutes after CBD intake. The initial blood sample served to ensure participant compliance (prior to first intervention) and medication washout prior to the second intervention in case participants received CBD during the first intervention. After collection, blood samples were immediately cooled at 4°C and kept cool until evaluation by the Institute of Forensic Medicine of the University of Basel within 7 days during the routine measurements performed by the institute.

Whole-blood samples were prepared using automated online solid-phase extraction and were analyzed by gas chromatography tandem mass spectrometry using a method adapted from previous analyses.[47,58] The method was fully validated according to the guidelines of the Society of Toxicological and Forensic Chemistry.[51,53] Besides CBD, cannabinol (CBN), THC, 11-hydroxy-tetrahydrocannabinol (OH-THC), and 11-nor-9-carboxy-THC (THC-COOH) were also quantified. Limits of detection were 0.25 μg/L for CBD, CBN, THC, and OH-THC, and 2.5 μg/L for THC-COOH, and limits of quantification were 0.5 μg/L for CBD, CBN, THC, and OH-THC and 5 μg/L for THC-COOH. Study staff performing the laboratory analyses were not blinded to the study medication (CBD or placebo) that was applied. In case of the placebo application, only the initial sample was analyzed.

2.9 Statistical analyses

Participant characteristics are shown as numbers (proportions), medians with interquartile ranges, and means ± SDs as appropriate (**Table 1**). The mean currents used are also presented as medians with interquartile ranges.

We quantified NRS, the area of hyperalgesia, and the area of allodynia using the mean ± SD over all measured time points. Mean differences in the area of hyperalgesia, area of allodynia and pain for CBD vs placebo were assessed by 2-sample, paired *t* tests. No adjustments for *P* values were made.

Differences in current at the first and second sessions were examined using a Wilcoxon signed-rank test, and differences in sex for area of hyperalgesia, area of allodynia, and NRS were examined using Wilcoxon–Mann–Whitney tests.

CBD concentrations measured at 200 minutes were plotted against the area of hyperalgesia, area of allodynia, and the NRS (from minute 140 to minute 200). The line of best fit from a least-squares linear regression, the *P* value for the CBD coefficient, and Pearson *r* were also reported. In addition, CBD concentrations measured at 200 minutes (presented as median [Q1, Q3]) against the area of hyperalgesia, the area of allodynia, and the NRS at 200 minutes were plotted.

Sample size was estimated to show a 20% decrease in hyperalgesia for CBD vs placebo in a paired *t* test using an α of 5% and a power of 90%. Our rationale was as follows: A recent study of our group revealed that a placebo application without deception is able to reduce the area of hyperalgesia about 20%.[57] Thus, the effect of CBD should be at least as strong as an intervention without a medically active component. Assuming a dropout rate of 10%, a total of at least 23 participants should be recruited in order to have 20 evaluable participants (**Fig. 1**).

3. Results

3.1. Baseline characteristics

Participants were recruited from May 2020 through September 2020. All participants (n = 24) were white European except for 1 Asian and 1 of mixed African and European ancestry, had a balanced male and female ratio, and were aged 18 to 54 years (mean age, 25 ± 7 years). Mean body mass index was 22.0 ± 1.9 kg/m^2 (**Table 1**).

Two participants were excluded from the study because of CBD in the basal blood sample, and one due to emotional distress during the intervention. These participants were replaced by newly recruited volunteers. Data of excluded participants were not analyzed. Complete data sets were available for 21 participants. Apart from 1 report of moderate nausea and a slight temporary decrease in oxygen saturation, no other relevant side effects occurred.

The median current used during the first and second interventions did not differ significantly (14.1 mA [Q1-Q3 = 9.3-17.4] vs 14.8 mA [Q1-Q3 = 10.3–18.5], $P = 0.794$, Wilcoxon signed-rank test).

3.2. Pain, hyperalgesia, and allodynia response

We compared NRS, area of hyperalgesia, and allodynia during the remifentanil infusion between 100 and 130 minutes for the period 140 to 200 minutes after infusion stopped (**Fig. 3**). There were significant increases in NRS (2.2 [1.4-3.3] vs 5.1 [4.4-5.7], $P < 0.001$), area of hyperalgesia (12.3 cm [4.5-25.4] vs 25.3 cm [15.1-39.6], $P < 0.001$), and area of allodynia (4.8 cm [1.7-9.1] vs 11.0 cm [5.2-23.8], $P = 0.003$). Furthermore, the area of hyperalgesia from 140 to 200 minutes significantly increased compared with baseline measurements (17.0 cm [8.1-28.7] vs 25.3 cm [15.1-39.6], $P = 0.013$). There was no significant difference between CBD or placebo on hyperalgesia, allodynia, or pain at any time point (**Fig. 3**).

Pain (NRS), area of hyperalgesia, and area of allodynia did not differ significantly between sexes: male (n = 11) vs female (n = 12) participants NRS 5.4 vs 4.7 ($P = 0.073$), area of hyperalgesia 25.5 vs 23.0 cm^2 ($P = 0.432$), and area of allodynia 16.1 vs 9.7 cm^2 ($P = 0.375$).

3.3. cannabidiol whole blood levels

The mean whole-blood concentration of CBD at 130 minutes was 4.1 ± 3.0 μg/L (mean ± SD), and at 200 minutes, it was 8.2 μg/L ± 6.9 μg/L (mean ± SD). Using Pearson *r* no significant correlation between CBD levels and hyperalgesia, allodynia or mean pain from minute 140 to minute 200 could be shown. The slight correlation was isolated to time point 200 minutes, but significance was not reached (**Fig. 4**).

Two participants were excluded and replaced due to CBD contamination in baseline blood sample. Apart from CBD, no other analyte (CBN, THC, THC-OH, and THC-COOH) was detected above their respective limits of detections in any of the whole-blood samples.

4. Discussion

In this prospective, randomized, double-blinded, placebo-controlled, crossover trial investigating healthy adults, the oral application of 1600-mg CBD in fasted state induced no effect on OIH, pain, and allodynia.

4.1. Pain model

Besides its broad reflection of pain processing, the strength of the model applied is the simultaneous assessment of local pain and central sensitization.[34] The model does not reflect the local inflammatory process on terminal nerve endings. Therefore, the local anti-inflammatory effects of CBD in the very periphery are beyond the scope of the study but are not of major interest in OIH.[14,42]

4.2. Clinical relevance

Despite growing awareness of OIH,[1,20,24,32] missing alternatives to strong opioids for intraoperative analgesia[19] reveal the need for opioid adjunct therapies to improve postoperative pain management by targeting OIH.

Besides the sparse evidence of CBD as a therapeutic in treatment of pain and hyperalgesia,[8,10] there is an enormous interest in over-the-counter CBD products.[37] More than 60% of consumers use CBD to treat medical conditions frequently associated with pain.[13]

CBD interacts with several receptors and intracellular messengers that have been identified as possible targets for the modulation of pain. Preclinical studies could show several antinociceptive effects on mechanical allodynia via the modulation of 5-HT1A-receptors,[18,29] anti-inflammatory, and antihyperalgesic potential in carrageenan-evoked thermal hyperalgesia,[14,54] and protection against paclitaxel-induced neuropathic pain.[73]

Recent research on the ability of CBD to antagonize σ-1-receptor revealed a potential target for the treatment of neuropathic pain.[55] Sánchez-Fernández et al. demonstrated that antagonizing the sigma-1 receptor enhanced periphery morphine-induced mechanical antinociception.[56] Sigma-1 receptors interact with both NMDARs and TRPV1 calcium channels,[28] which play a key role in modulating nociceptive pathways and are a promising approach to counteract OIH. Although Pernia-Andrade et al.[52] could decrease hyperalgesic and allodynic skin area with a CB1-receptor antagonist in human, trials on CBD in acute pain in humans are scarce. Despite identification of these targets in preclinical studies, we could not show any effect on OIH. The following points have to be addressed.

4.3. Route of administration, dose, and pharmacokinetics

Cannabidiol (Epidiolex) is approved by the US Food and Drug Administration for treating certain forms of epilepsy in patients, so far for oral use only.[28] Determining the optimal dose for a possible analgesic and antihyperalgesic effect of CBD in combination with remifentanil was, thus, not possible. We aimed for the highest recommended maintenance dosage of 20 mg/kg/d[28] Manini et al. investigated the safety of different oral CBD doses administered together with intravenous fentanyl in humans up to 800 mg only, which was described as safe and well tolerated.[43]

In a recent review, Millar et al.[49] commented that effective dosing of CBD varied greatly from <1 to 50 mg/kg/d, depending on measured outcome. Daily doses of 600- to 1000-mg CBD were effective as an adjunct and independent treatment of schizophrenia[7,45] and produced significant effects on functional brain areas documented via functional magnet resonance imaging[5] without major side effects.

Previous preclinical data about the effectiveness of CBD on hyperalgesia and pain are inconsistent. Costa et al. used similar doses (20 mg/kg) to investigate antihyperalgesic properties of CBD in rats. While showing anti-inflammatory effects during repetitive dosing, single doses of 20 mg/kg had no effect on nociceptive thresholds in animal trials.[16] In contrast, Rock et al.[54] found an antihyperalgesic effect of 10 mg/kg orally administered CBD 60 minutes prior to carrageenan-evoked inflammatory peripheral pain.

Costa et al. measured the dose-dependent anti-inflammatory and antihyperalgesic effect of CBD after carrageenan infiltration of rat paws 1 hour after CBD administration. Lower doses of 5 to 7.5

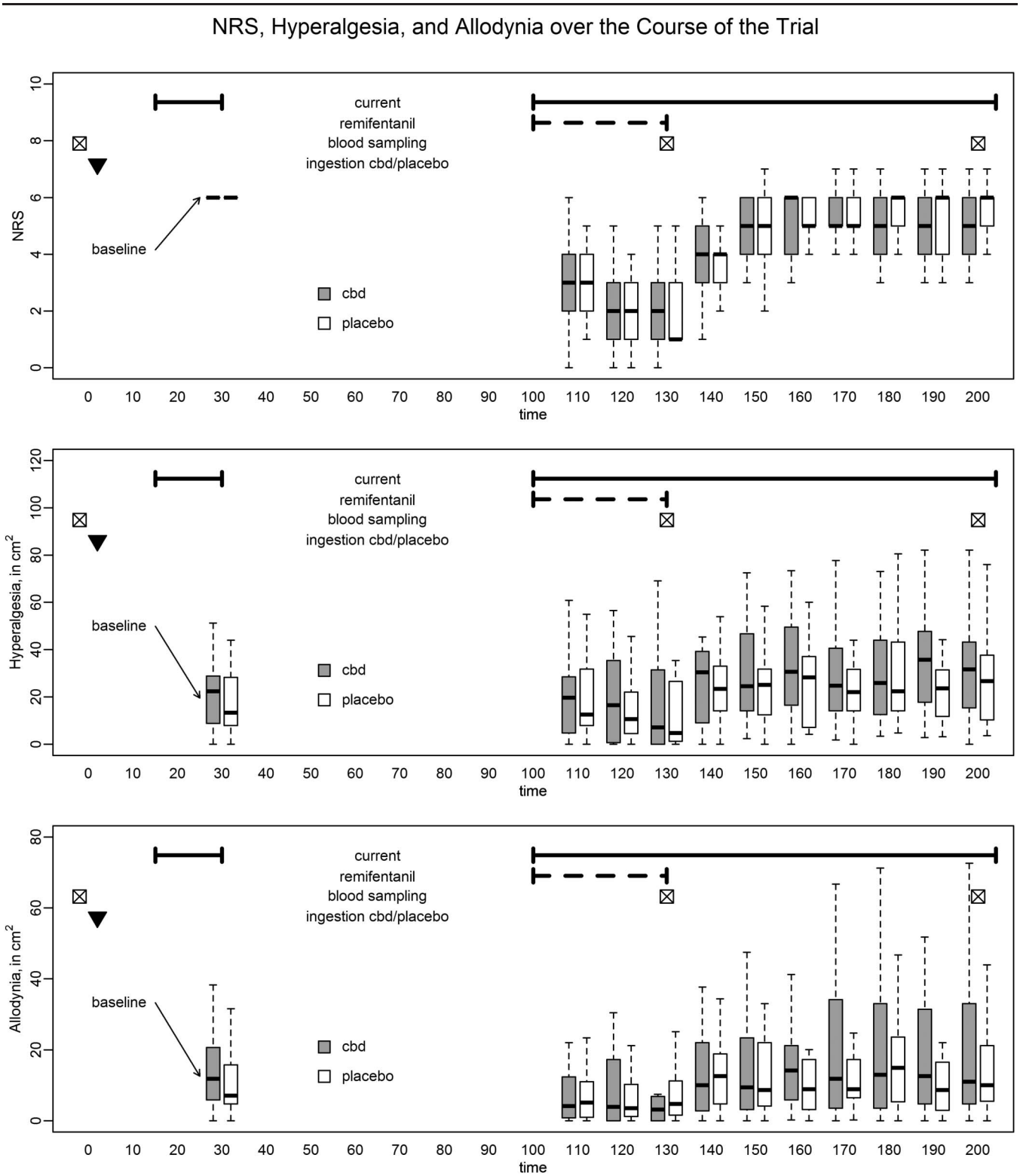

Figure 3. Outcome variable of intradermal electrical stimulation over time. All values are represented as box-plots (whiskers display minimum and maximum values). CBD, cannabidiol; NRS, numeric rating scale.

mg/kg required repetitive dosing, but single doses of 10 to 40 mg/kg were sufficient to stop hyperalgesia.[14] However, due to the differences in models (eg, outcome-measures: behavior vs NRS) and pharmacokinetics, preclinical dose response studies cannot be transmitted one-to-one to clinical studies.[63] Overall, reliable models of dose-concentration effect in humans are missing.[39]

4.4. Cannabidiol whole-blood levels

Our blood samples were analyzed by the Institute for Forensic Medicine of the University of Basel. According to their standards (conditions of Swiss traffic law), all measurements are done using whole blood. The blood/plasma (b/p) ratio of CBD has not been

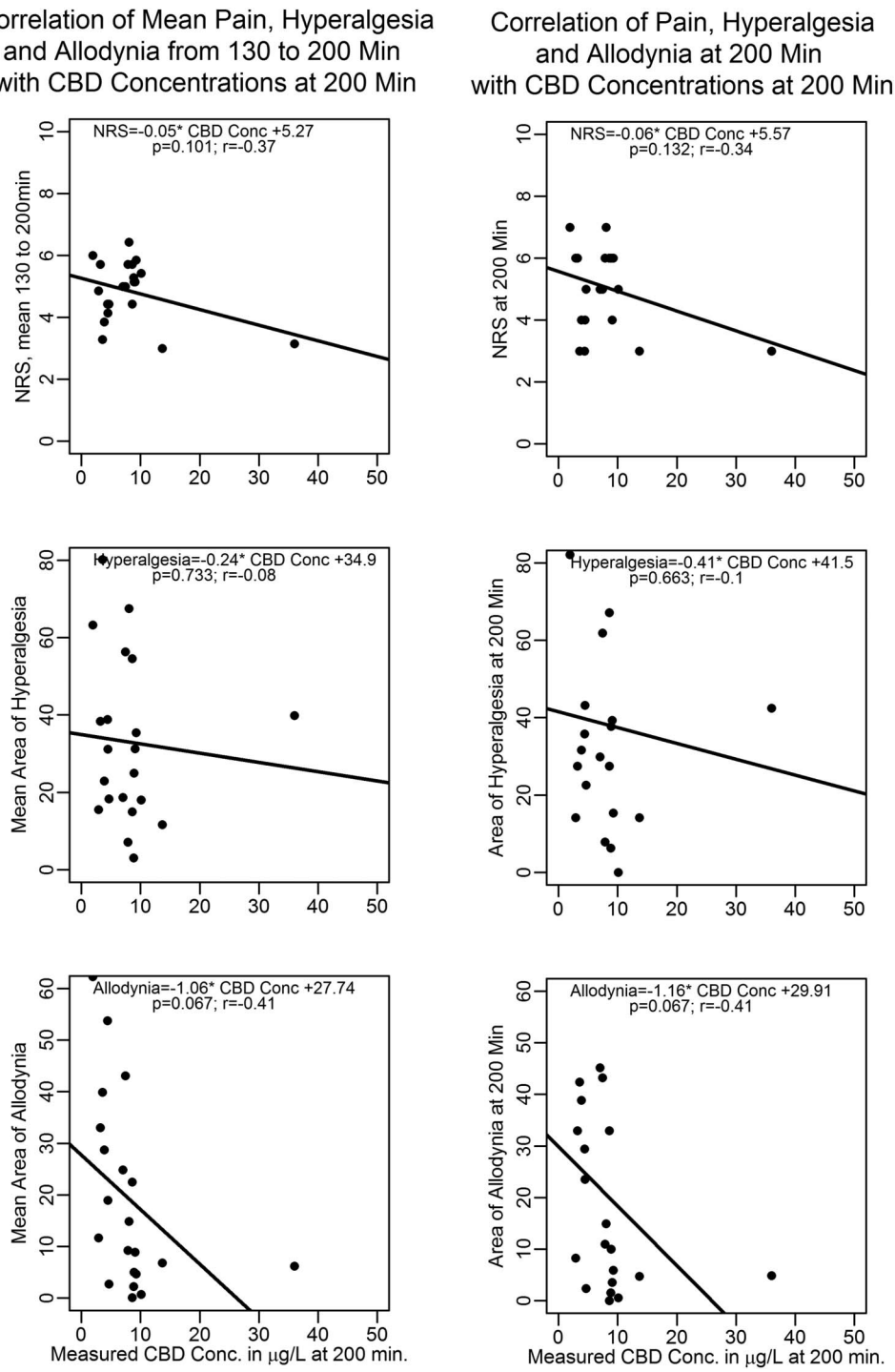

Figure 4. The left panel shows the relationship between the measured CBD concentration at the time point 200 minutes with the average pain score (NRS), area of hyperalgesia, and allodynia *over time*. The right panel shows the relationship between the measured CBD concentration at the time point 200 minutes with the pain score (NRS), area of hyperalgesia, and area of allodynia *at the same time point (200 min).* CBD, cannabidiol; conc, concentration; NRS, numeric rating scale; *r*, Pearson correlation coefficient.

thoroughly examined. However, b/p-ratios of the structurally related THC of 0.39 to 0.63 have been reported.[23,60] Furthermore, Schwope et al. examined whole-blood and plasma levels of several cannabinoids after smoking of cannabis. Regarding peak concentrations of CBD, the authors reported means of 2.1 μg/L in whole blood and 3.4 μg/L in plasma. These levels would correspond to a b/p-ratio of approximately 0.62, suggesting a similar pattern as for THC. However, conclusive data on whole-blood levels of CBD after oral ingestion as well as b/p-ratios are missing. Additionally, reports on CBD plasma levels often lack detailed information on blood collection tubes,[68] sample preparation,[26] and method of analysis,[59] therefore rendering comparison of our data to reported plasma levels even more difficult.[64]

Overall, there is a lack of dose-ranging studies.[49] Information on the dose given and achieved plasma levels vary greatly

between studies.[7,27,43,67] Furthermore, interindividual variance in medication uptake is high. For example, in a study by Haney et al.[27] peak plasma levels ranged from 1.6 to 271.9 μg/mL after oral administration of 800-mg CBD. According to the prescribing information of pure CBD (Epidiolex) and Taylor et al., the coadministration of CBD with a high-fat/high-calorie meal would increases maximal concentrations by 5-fold and area under the curve by 4-fold.[28,68] This was confirmed by several studies.[6,17,64,75] In all of the above-cited studies, CBD was taken with food. In a preliminary study of our group,[58] we used a single dose of 800-mg CBD and measured a median whole-blood CBD level of 5 μg/L [Q1-Q3 = 4-10.4 μg/L] 130 minutes after ingestion.[58] When administering a double dose of (1600 mg) CBD, we found no significantly different levels at the same time point. This is in accordance with a review by Millar et al.[50] suggesting a saturation effect between 400 and 800 mg. We assume that the CBD passed the gastrointestinal tract without additional resorption,[72] and solubility-limited uptake is occurring given the lipophilic nature of CBD.[68]

Two participants were excluded from our analyses due to CBD in the control blood sample. No anamnestic abnormalities were detected, and the laboratory did not find any contamination with THC metabolites. Acknowledging the high variability in half-life, we assume that these participants were slow metabolizers and had residual CBD from the first meeting.[49,50] One of the 2 reached 400 μg/L CBD level at 200 minutes during the first intervention (**Fig. 4**). We have no conclusive explanation for this outlier.

4.5. Strength and limitations

Our research approach was based on a well-established pain model, which produced stable OIH like already demonstrated in several studies.[2,33,35,44,70] The experiment was designed as a prospective, randomized, placebo-controlled, double-blinded, crossover study, with a study population balanced according to sex.

We were well aware of the poor bioavailability of orally administered CBD. Regarding the low whole-blood levels of CANAB I,[58] we increased the CBD dose and according to the limits of safe dosing reported in the literature. Referring to Haney et al.,[27] we postponed the observational period compared with CANAB I by 70 minutes to increase the likelihood to cover the CBD plasma peak. Further studies report peaks between 4 and 6 hours,[17,38] so we have to address, that we still might have missed peaks, during our observation.

Despite knowing the desired effect of serving food with CBD, we insisted on an empty stomach prior to and during the intervention to achieve equal conditions and even more to ensure maximal safety by minimizing the risk of aspiration due to remifentanil. We decided against repetitive dosing because this would not be transferable to the clinic of acute pain or premedication prior to anaesthesia. Preferred intravenous administration was not available at the time; Meyer et al. recently published an article on intravenous CBD application in human.[48]

Kathmann et al. showed that CBD is an allosteric modulator of mu- and delta-opioid receptors on rat cerebral cortex membrane homogenates, but very high concentrations were needed for this effect. They doubt that in vivo conditions such CBD levels could be achieved.[31] Likewise, Rodriguez-Munoz et al.[55] injected their CBD intracerebroventricularly and had promising results in diminishing the influence of glutamate NMDA receptors. We cannot rule out that we possibly missed the required drug levels to achieve an effect. On the other hand, 17.0 μg/L (SD 29.0) in whole-blood level 120 minutes after ingestion of CBD significantly affected the activation of brain areas in functional magnet resonance imaging in previous studies.[7]

5. Conclusion

CBD at a high single oral dose of 1600 mg is not effective in reducing OIH. Before neglecting the effect of CBD on OIH, research should focus on drug formulations that enable higher drug levels after single dosing (eg, intravenous application) or aim for indications where repetitive administration is suitable. Based on our results, a single oral dose in fasted state cannot be recommended as a therapeutic to prevent OIH in the perioperative setting.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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