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ORIGINAL ARTICLE

Effect profile of paracetamol, $\Delta 9$ -THC and promethazine using an evoked pain test battery in healthy subjects

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No financial funding was received to perform the clinical study. Echo Pharmaceuticals unconditionally provided $\Delta 9$ -THC (Namisol®) and matched placebo tablets.

Conflicts of interest

Centre for Human Drug Research has developed the battery of evoked pain tasks (PainCart) for use in early-phase clinical trials.

Originality statement

This manuscript contains original work and has not been presented anywhere else.

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Abstract

Background: A battery of evoked pain tasks (PainCart) was developed to investigate the pharmacodynamic properties of novel analgesics in early-phase clinical research. As part of its clinical validation, compounds with different pharmacological mechanisms of actions are investigated. The aim was to investigate the analgesic effects of classic and nonclassic analgesics compared to a sedating negative control in a randomized placebo-controlled crossover study in 24 healthy volunteers using the PainCart.

Methods: The PainCart consisted of pain tasks eliciting electrical, pressure, heat, cold and inflammatory pain. Subjective scales for cognitive functioning and psychotomimetic effects were included. Subjects were administered each of the following oral treatments: paracetamol (1000 mg), $\Delta 9$ -THC (10 mg), promethazine (50 mg) or matching placebo. Pharmacodynamic measurements were performed at baseline and repeated up to 10 h postdose.

Results: Paracetamol did not show a significant reduction in pain sensation or subjective cognitive functioning compared to placebo. Promethazine induced a statistically significant reduction in PTT for cold pressor and pressure stimulation. Furthermore, reduced subjective alertness was observed. $\Delta 9$ -THC showed a statistically significant decrease in PTT for electrical and pressure stimulation. $\Delta 9$ -THC also demonstrated subjective effects, including changes in alertness and calmness, as well as feeling high and psychotomimetic effects.

Conclusions: This study found a decreased pain tolerance due to $\Delta 9$ -THC and promethazine, or lack thereof, using an evoked pain task battery. Pain thresholds following paracetamol administration remained unchanged, which may be due to insufficient statistical power. We showed that pain thresholds determined using this pain test battery are not driven by sedation.

Significance: The multimodal battery of evoked pain tasks utilized in this study may play an important role in early-phase clinical drug development. This battery of pain tasks is not sensitive to the effects of sedation alone, and thus suitable to investigate the analgesic potential of novel analgesic compounds.

1. Introduction

The complex clinical reality of pain medicine demands novel therapeutics. A multimodal battery

of evoked pain tasks could be a useful tool to investigate the analgesic properties of novel compounds, but needs to be pharmacologically validated for specific classes of compounds. In this study, the

effects of three oral drugs were investigated and compared to placebo: Δ 9-tetrahydrocannabinol (Δ 9-THC), paracetamol and promethazine.

Different cannabinoids have previously been shown to be effective in various pain conditions, including neuropathic pain related to oncological disease (Vadalouca et al., 2012). Δ 9-THC has been shown to be an effective analgesic in preclinical studies and clinical trials. However, previous formulations of cannabinoid Δ 9-THC are also known for variable pharmacokinetic profiles and pharmacodynamic responses (Huestis, 2007). To overcome barriers in clinical application, novel formulations and cannabinoids are under development (Klumpers et al., 2012).

Even though paracetamol is one of the most widely used medications in the world, there is still debate regarding its exact mechanism of action. Paracetamol is thought to be a weak inhibitor of prostaglandins (PG) synthesis. The subsequent main driving mechanism of paracetamol analgesia is not completely understood. It has been proposed that it exerts most of its effects through COX-2 inhibition, but also inhibition of endocannabinoids has been proposed. In addition, various neurotransmitter systems (e.g. serotonergic, opioid and noradrenaline) are thought to be involved (Bertolini et al., 2006; Graham et al., 2013; Koppel et al., 2014; Boychuk et al., 2015).

To investigate the role of sedation rather than analgesic effects of psychoactive compounds, a negative control was included in this study in the form of the H1 antihistaminergic promethazine (50 mg). Even though it has been observed in preclinical research that H1 antihistaminergic drugs may have analgesic potential, this has not been replicated in clinical practice for oral formulations administered alone (Rumore and Schlichting, 1985; Raffa, 2001). Therefore, we considered this sedative compound suitable as a comparator drug without analgesic effects.

The primary aim of this study was to investigate the analgesic effects of classic and nonclassic analgesics compared to a sedating negative control in a randomized placebo-controlled crossover study in 24 healthy volunteers using the PainCart. As a secondary objective, by comparing the effects of the three compounds within each subject in a crossover design, and comparing the analgesic profile to the profiles of other analgesic compounds that we recently investigated using the battery of evoked pain tasks, we aimed to further elucidate the still unknown pharmacological mechanism of action of Δ 9-THC and paracetamol analgesia.

The battery of evoked pain tasks has been pharmacologically validated by investigating a broad range of analgesics from various classes, with diverse but well-known mechanisms of action (Okkerse et al., 2016d). This first pharmacological validation study demonstrated the necessity of utilizing a range of pain tasks in early-phase drug research. Namely, each compound provided a unique fingerprint of effects on the test battery. These findings emphasized the importance of utilizing a range of pain tasks, rather than a single pain task, when determining the profile of analgesic effects of a compound in early-phase drug development. Building on this knowledge, this study investigated the effects of two (classes of) analgesics, paracetamol and Δ 9-THC, and additionally the effects of sedation using promethazine as a negative control.

2. Methods

2.1 Subjects and study design

The study was a double-blind, double-dummy, single dose, randomized, placebo-controlled, crossover study in which the effects of paracetamol, Δ 9-THC and the negative control promethazine were compared to placebo. The study was conducted at the Centre for Human Drug Research in Leiden, the Netherlands. The study was approved by the Medical Ethics Committee of Stichting Beoordeling Ethiek Biomedisch Onderzoek (Assen, the Netherlands) and was conducted according to the Dutch Act on Medical Research Involving Human Subjects (WMO) and in compliance with all International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. This study was registered in the public registry of the Centrale Commissie Medisch Onderzoek (CCMO) in the Netherlands, under registration number: NL54643.056.15.

Each subject provided written informed consent before any screening procedures were performed. A total of 24 healthy subjects (12 men and 12 women) between 18 and 45 years of age with a body mass index of 18 to 30 kg/m² were enrolled. The subjects underwent a full medical screening, including medical history anamnesis, a physical examination, blood chemistry and haematology, urinalysis, electrocardiogram (ECG) and assessment of the minimal erythema dose (MED) for ultraviolet B (UVB) light to assess eligibility. Subjects with a clinically significant known medical condition, in particular any existing condition that would affect sensitivity to cold or

pain, were excluded. Subjects with Fitzpatrick skin type V or VI, widespread acne, tattoos or scarring on the back were excluded due to the inability to accurately assess MED. Also any subject, who was a regular user of any illicit drugs, had a history of drug abuse or a positive drug screen at screening was excluded. Smoking and the use of xanthine-containing products were not allowed during dosing days. Alcohol was not allowed at least 24 h before each scheduled visit and during the stay in the research unit.

2.2 Study drugs

Paracetamol (1000 mg), $\Delta 9$ -THC (10 mg), promethazine (50 mg) or placebo were given as a single dose. Paracetamol 1000 mg is within the labelled dose range in the European Union (EU) and has been shown to be effective in reducing various types of pain. The currently used formulation of $\Delta 9$ -THC (Namisol[®], Echo Pharmaceuticals) has been administered in multiple studies including healthy volunteers (Klumpers et al., 2012) and different patient populations (Ahmed et al., 2014; Utomo et al., 2015; van Amerongen et al., 2017). $\Delta 9$ -THC has potential side effects, but is generally considered well-tolerated, even in high dosages. Promethazine is a classic H1-antihistamine with some anticholinergic effects. Daily doses up to 150 mg are prescribed for the treatment of allergic rhinitis and motion sickness. Single doses up to 50 mg are prescribed to induce mild sedation.

Due to unequal formulations ($\Delta 9$ -THC was formulated as an oral tablet, whereas paracetamol and promethazine were formulated as capsules), matched placebo tablets for each treatment were administered in a double-dummy fashion to maintain blinding of treatment for participants and researchers.

2.3 Pharmacodynamic assessments

Pain detection and tolerance thresholds were measured using a battery of evoked pain tasks, as described previously (Hay et al., 2016; Okkerse et al., 2016a,b,c,d). The test battery consists of an integrated range of pain tasks for measuring different modalities of pain. Assessments were conducted twice predose (double baseline) and 0.5, 1, 2, 3, 4, 6, 8 and 10 h postdose by trained personnel. Each measurement round was performed in a fixed order and took approximately 30 min to complete. To eliminate the risk of tissue damage, all pain tasks had a maximum safety cut-off. The aim of the test battery is to assess as objectively as possible the

levels of pain induced by different noxious mechanisms in human subjects. A training session was included as part of the screening examination to reduce learning effects during the study and exclude nonresponders (i.e. subjects who reach PDT at >80% of the maximum at any of the nociceptive tasks, excluding the heat pain task) or extreme responders (subjects indicating to be intolerable to any of the nociceptive tasks). All measurements were performed in a quiet room with ambient illumination. Per session, there was only one subject present in the same room. To reduce variability from affects associated with fear of pain, the subjects themselves were responsible for starting and ending each pain task.

The battery of evoked pain tasks consists of the following tasks for nociception: the electrical stimulation task, pressure stimulation task, thermal (heat) pain and the cold pressor tasks. Furthermore, the test battery includes a model for inflammatory pain, the UVB model and a paradigm to quantify conditioned pain modulation (CPM), formerly known as Diffuse Noxious Inhibitory Control (DNIC).

For the electrical stimulation task, the pressure stimulation task and the cold pressor task, pain intensity was measured continuously (beginning from when the first stimulus was applied until the end of the test) using an electronic visual analogue scale (eVAS) scale ranging from 0 (no pain) to 100 (most intense pain tolerable). Equipment was programmed to cease giving stimuli if the recorded pain intensity reaches the maximum pain score (100) or when the maximum safety level was reached. For the abovementioned pain tasks, the pain detection threshold (PDT) (defined as eVAS score >0), pain tolerance threshold (PTT) (defined as eVAS score of 100) and Area Under the Curve (AUC) or Area Above the Curve (AAC) (cold pressor only) were determined. Additionally, a post-test Visual Analogue Scale (VAS) score (anchored with no pain (0) and worst pain imaginable (100)) was performed to retrospectively assess the worst pain experienced during the pain task. For the thermal pain task (normal skin and UVB exposed skin), only the (average of triplicate) PDT was determined, since assessment of heat PTT is prone to inducing tissue damage. For all nociceptive tasks, except the thermal pain tasks, the primary endpoint is PTT. For the thermal pain tasks (normal skin and UVB exposed skin), the PDT is the primary endpoint of the measurement. However, since each parameter (PDT, PTT, AUC/AAC) provides information on different aspects of the nociceptive system

and pain perception, all variables are taken into account.

In addition to the evoked pain tasks, subjective assessment of sedation and psychotomimetic effects were included as PD outcome measures. Visual analogue scales (VAS) as originally described by Norris (Norris, 1971) have often been used previously to quantify subjective effects of a variety of sedative agents (Norris, 1971; de Visser et al., 2001). A set of VAS scales assessing alertness, mood and calmness (Bond and Lader) (Bond and Lader, 1974) were used for subjective assessment of sedation. The VAS allows the subjects to evaluate their current subjective states. Each VAS scale consists of two words representing opposite feelings placed to the left and right of a horizontal line. The subject is asked to mark his/her current feelings. Subjective psychotomimetic (psychedelic) effects were evaluated using VAS Bowdle. This scale has been used extensively to quantify subjective psychotomimetic effects of psychoactive compounds, including ketamine (Bowdle et al., 1998). Bowdle Psychotomimetic Effects Scores consist of thirteen visual analogue lines ranging from 0 ('not at all') to 100 ('extremely') (van Steveninck, 1993), addressing various (abnormal) states of mind.

2.4 Sample size and randomization

Based on literature, PDT for the cold pressor assessment was used for the sample size calculation as this assessment has been shown sensitive to the effects of $\Delta 9$ -THC in previous research (Cooper et al., 2013). For the cold PDT, a sample size of 24 subjects has 80% power to detect a difference in means of 35%, assuming a standard deviation of differences of 0.5, using a paired *t*-test with a 0.05 two-sided significance level. For the sample size calculation, placebo data from a previous study with the battery of pain tasks were used to determine variability (Okkerse et al., 2016d). The balanced Williams design randomization code was generated using SAS version 9.1.3 by a study-independent statistician.

2.5 Statistical analysis

To establish whether significant treatment effects could be detected on the PD outcome variables, variables were analysed with a mixed model analysis of variance with treatment, time, sex, treatment by time and treatment by sex as fixed factors and subject, subject by treatment and subject by time as random factors and the average baseline measurement as covariate. The Kenward–Roger approximation was used to estimate denominator degrees of freedom,

and model parameters were estimated using the restricted maximum likelihood method. The general treatment effect and specific contrasts were reported with the estimated difference and the 95% confidence interval, the least square mean estimates and the *p*-value. Graphs of the least squares means estimates over time by treatment were presented with 95% confidence intervals as error bars. All calculations of the pharmacodynamic parameters were performed using SAS for Windows version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The main SAS procedure that was used in the analysis was 'PROC MIXED'. No adjustments for multiple comparisons were employed. The contrasts for the relevant time periods based on the expected PK profiles of the compounds of 0–4 h are presented.

3. Results

A total of 25 subjects were randomized, of which 23 subjects completed study participation. Two (2) subjects withdrew consent to participate for personal reasons, one of which was replaced. A summary of the baseline demographics is provided in Table 1.

3.1 Pharmacodynamics

Time profiles of the pharmacodynamic responses on PTT for each pain task, except heat pain (Normal

Table 1 Summary demographic and baseline characteristics for all subjects (*n* = 25).

Age (years)	
Mean (SD)	24.0 (5.6)
Median	23
Min, Max	18, 45
BMI (kg/m ²)	
Mean (SD)	23.5 (2.9)
Median	23.7
Min, Max	18.2, 29
Sex (<i>n</i>)	
Female (%)	12 (48%)
Male (%)	13 (52%)
Race	
Other	1 (4%)
White	24 (96%)
Fitzpatrick skin type	
II: Always burns and tans minimally	6 (24%)
III: Burns moderate and tan gradually	11 (44%)
IV: Burns minimally and tans well	8 (32%)
MED (mJ/cm)	
Mean (SD)	777 (249)
Median	702
Min, Max	351, 1321

BMI, body mass index; MED, minimal erythema dose.

skin and UVB skin) for which PDT is displayed, are presented in Fig. 1. This figure also includes a graphical presentation of CPM (Delta PTT for electrical pain). PTT and PDT measurements were log (ln) transformed before analysis, due to the log normal distribution of the data. The results are presented as % change from baseline over a 10-h period. A detailed description of the results of the least square means (LSM) analyses for each treatment as well as contrasts compared to placebo (0–4 h) can be found in Table 2. The results of the LSM analyses for the primary endpoints (PTT) are summarized in Fig. 2. Each spoke represents one of the pain tasks, resulting in an effect profile compared to placebo per treatment. Here, the dashed placebo line represents the value to which other treatment effects are normalized. A contrast distal from placebo indicates that the LSM PTT for that treatment is greater than placebo, proximal indicates a LSM PTT lower than placebo.

Furthermore, the results for the subjective scales for cognitive functioning and psychotomimetic symptoms are presented in Table 3. Paracetamol did not show a significant reduction in pain sensation compared to placebo. A small increase in AUC ($p = 0.0314$) was observed for the pressure pain task, indicating a slight increase in perceived pain

sensation. Treatment with paracetamol did not lead to any observable changes in subjective cognitive functioning or mood. Promethazine demonstrated a statistically significant reduction in PTT for the cold pressor pain task ($p = 0.0189$) and for the pressure stimulation task ($p = 0.0149$), as well as an increase in AUC ($p = 0.0032$), indicating an increase in pain sensation. In addition to the pharmacodynamic effects of promethazine on the pain task battery, a reduction in subjective alertness ($p = 0.0002$) was observed. $\Delta 9$ -THC did not show a statistically significant analgesic effect on any of the pain tasks. For the electrical stimulation task, the PTT was significantly decreased by -12.7% , ($p = 0.0134$), also indicating an increase in pain sensation. Furthermore, a significant reduction was observed for the pressure stimulation task PTT ($p = 0.0126$) and AUC ($p = 0.0001$). In addition to the effects observed on the pain task battery, $\Delta 9$ -THC also demonstrated other pharmacodynamic effects, including a reduction on the composite scale for alertness ($p < 0.0001$) and an increase on the composite scale for calmness ($p < 0.0001$) compared to placebo. Moreover, significant psychotomimetic effects were observed expressed in changes in internal perception ($p < 0.0001$) and external perception ($p < 0.0001$), measured using the VAS Bowdle, as

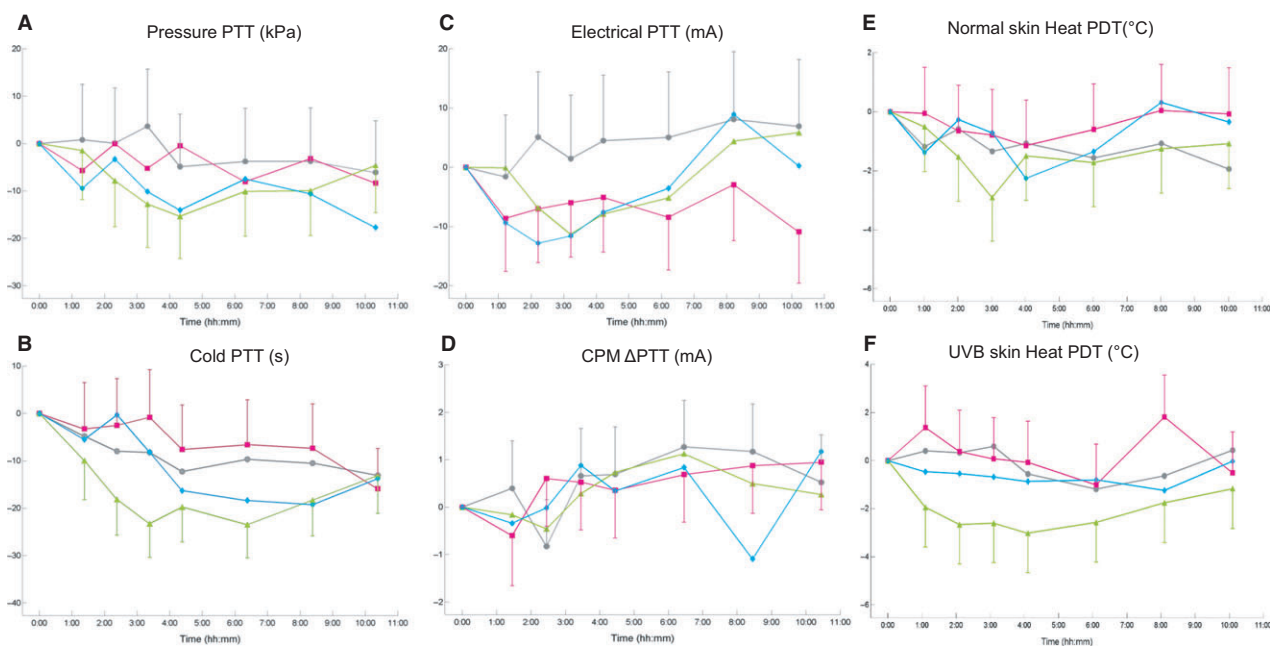


Figure 1 Overview of change from baseline time profiles for battery of evoked pain tasks. (A) pressure pain task in kPa (PTT); (B) cold pressor in s (PTT); (C) electrical pain task in mA (PTT); (D) conditioned pain modulation (CPM) in delta mA (PTT); (E) thermal pain normal skin in $^{\circ}$ C (PDT); (F) thermal pain UVB skin in $^{\circ}$ C (PDT). Lines with Circles (●) = placebo; lines with squares (■) = paracetamol; lines with triangles (▲) = promethazine; lines with diamonds (◆) = $\Delta 9$ -THC. Abbreviations: PTT, pain tolerance threshold; PDT, pain detection threshold.

Table 2 Summary of LSM analyses for battery of evoked pain tasks.

Endpoint	Placebo (n = 24) LSMean (95%CI)	Paracetamol (n = 23) Contrastr vs. placebo ^a (95%CI)	Promethazine (n = 23) Contrastr vs. placebo (95%CI)	Δ9-THC (n = 24) Contrastr vs. placebo (95%CI)
Cold pressor (s)				
PTT	13.4 (12.5–14.3)	5.2% (–4.6%, 16.0%) p = 0.3090	–11.1% (–19.3%, –1.9%) p = 0.0189	2.5% (–7.0%, 12.9%) p = 0.6183
PDT	3.2 (2.5–4)	3.5% (–15.0%, 26.0%) p = 0.7292	–17.0% (–31.8%, 1.2%) p = 0.0648	–0.8% (–18.5%, 20.7%) p = 0.9335
AAC	860 (803–922)	7.8% (–3.8%, 20.9%) p = 0.1938	–10.6% (–20.2%, 0.2%) p = 0.0548	4.1% (–7.0%, 16.6%) p = 0.4806
VAS	56.9 (52.8–61)	2.59 (–0.45, 5.63) p = 0.0940	1.48 (–1.56, 4.52) p = 0.3366	0.11 (–2.93, 3.15) p = 0.9444
Electrical stimulation (mA)				
PTT	22.1 (20.3–24.1)	–8.7% (–18.2%, 1.9%) p = 0.1023	–7.7% (–17.2%, 3.0%) p = 0.1495	–12.7% (–21.5%, –2.8%) p = 0.0134
PDT	9.43 (8.44–10.53)	–9.9% (–22.8%, 5.3%) p = 0.1896	0.8% (–13.7%, 17.8%) p = 0.9211	–2.7% (–16.6%, 13.4%) p = 0.7222
AUC	3244 (3112–3376)	171.37 (–21.12, 363.87) p = 0.0805	76.86 (–115.81, 269.53) p = 0.4311	196.58 (6.98, 386.19) p = 0.0423
VAS	54.6 (51.8–57.4)	1.71 (–1.18, 4.61) p = 0.2414	–1.38 (–4.28, 1.52) p = 0.3467	–0.68 (–3.53, 2.17) p = 0.6372
CPM: Electrical stimulation (mA)				
PTT	1.07 (0.64–1.51)	0.101 (–0.772, 0.973) p = 0.8206	–0.186 (–1.050, 0.678) p = 0.6716	0.099 (–0.785, 0.983) p = 0.8254
PDT	1.24 (0.62–1.87)	0.678 (–0.566, 1.921) p = 0.2841	0.052 (–1.186, 1.290) p = 0.9339	–0.144 (–1.398, 1.109) p = 0.8206
AUC	–147 (–192 to –102)	–24.74 (–107.64, 58.17) p = 0.5574	13.44 (–69.10, 95.98) p = 0.7488	9.63 (–73.60, 92.87) p = 0.8200
VAS	2.60 (1.95–3.47)	9.7% (–24.5%, 59.4%) p = 0.6238	16.5% (–18.8%, 67.1%) p = 0.4044	–1.7% (–32.8%, 44.0%) p = 0.9311
Pressure stimulation (kPa)				
PTT	39.9 (36.3–43.9)	–5.1% (–11.9%, 2.2%) p = 0.1653	–8.9% (–15.4%, –1.8%) p = 0.0149	–9.0% (–15.6%, –2.0%) p = 0.0126
PDT	16.7 (14.2–19.6)	–8.5% (–19.1%, 3.5%) p = 0.1552	–7.1% (–17.8%, 5.1%) p = 0.2392	–9.9% (–20.3%, 1.9%) p = 0.0972
AUC	6761 (6457–7064)	248.01 (22.33, 473.69) p = 0.0314	341.93 (115.96, 567.89) p = 0.0032	446.38 (221.09, 671.67) p = 0.0001
VAS	50.2 (44.2–56.2)	1.12 (–1.60, 3.85) p = 0.4176	–0.20 (–2.92, 2.52) p = 0.8841	0.35 (–2.35, 3.06) p = 0.7964
Normal heat (°C)				
PDT	45.1 (44.7–45.6)	0.5% (–0.9%, 2.0%) p = 0.4434	–0.6% (–2.0%, 0.8%) p = 0.3830	0.3% (–1.1%, 1.7%) p = 0.7229
UVB heat (°C)	39.7 (39.1–40.2)	0.2% (–1.1%, 1.4%) p = 0.8033	–2.8% (–4.1%, –1.6%) p = <0.0001	–1.0% (–2.3%, 0.3%) p = 0.1220

PTT, pain tolerance threshold; PDT, pain detection threshold; AAC, area above the curve; AUC, area under the curve; VAS, visual analogue scale; CPM, conditioned pain modulation.

^aContrastrs over 0–4 h post dose.

Bold values signify that the p-value <0.05

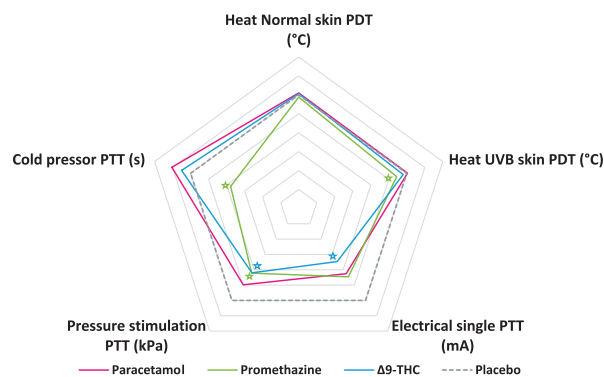


Figure 2 Spider plot overview of pharmacodynamic response profile for battery of evoked pain tasks normalized to placebo (0–4 h). Dashed placebo line represents the value to which other treatment effects are normalized. Distal from placebo indicates least square mean PTT greater than placebo, proximal indicates least square mean PTT lower than placebo. Actual values are described in Table 2. A star (★) indicates a statistically significant ($p < 0.05$) difference compared to placebo for treatment on pain task.

well as VAS Feeling high ($p = <0.0001$). Of note, psychotomimetic effects were virtually absent after placebo treatment, thereby leading to high significance levels even at small effect sizes.

3.2 Safety

During the execution of this study, a total of 79 Treatment Emergent Adverse Events (TEAE's) were registered. The majority ($n = 43$, 54%) of these were recorded after treatment with $\Delta 9$ -THC, after which 20 of 25 subjects reported any event. Out of all TEAE's, seven (8.8%) were considered moderate, all others were deemed mild. For $\Delta 9$ -THC treatment, 60% of subjects reported an adverse event in the system organ class (SOC) Nervous system disorders, most of which were dizziness (40%) and headache (20%). Furthermore, three subjects (12%) reported euphoric mood and three subjects (12%) mild auditory hallucinations. A total of four subjects experienced TEAE's of moderate intensity after treatment with $\Delta 9$ -THC, leading to one or more missing measurement. For treatment with promethazine, most prominently somnolence ($n = 7$, 30.4%) and fatigue ($n = 6$, 26.1%) were observed. For paracetamol treatment, a total of six events were recorded, which is comparable to placebo treatment.

To investigate whether adverse events may have impacted the outcome of the pain tasks, a subgroup analysis was performed in which the four subjects that experienced at least one adverse event of moderate intensity were omitted from the analyses, as a

moderate adverse event may have impacted pain tasks adjacent to its occurrence. This analysis had no significant impact on the interpretation of the results; therefore, it was decided to report the results on the intention-to-treat (ITT) population.

4. Discussion

The main objective of the present study was to investigate the effects of a classical (paracetamol) and a nonclassical ($\Delta 9$ -THC) analgesic on a battery of pain tasks (PainCart[®]), compared to placebo and a negative control (promethazine). The effects of the different treatment effects on each pain task are summarized in Fig. 2, demonstrating the differential effect profile of each compound for the different pain tasks. Contrary to our expectation, we found that paracetamol was not effective at reducing any of the pain modalities measured using the battery of evoked pain tasks. Furthermore, $\Delta 9$ -THC did not show any acute analgesic effect, and even showed a hyperalgesic effect on two of five pain tasks, namely electrical and pressure pain. Finally, the negative control promethazine showed an increase in pain sensation for cold, pressure and inflammatory pain. In addition to the pain tasks, cognitive tests were performed to assess subjective alertness, mood and psychotomimetic symptoms, which were moderately affected by treatment with $\Delta 9$ -THC (alertness, calmness, internal and external perception) or promethazine (alertness).

This study did not demonstrate an acute analgesic effect of $\Delta 9$ -THC, even though the subjective psychoactive effects were clearly present. As such we can conclude that the subjective psychoactive effects are not responsible for producing nociceptive analgesia. Moreover, the present study helped to further elucidate the mechanism of action of paracetamol as our results enable comparison to other analgesics with known mechanisms of action. Finally, when combining the findings of the current study with the existing body of evidence from this battery of evoked pain tasks, we have shown this battery to be a robust tool to determine analgesic effects that are specific, and thus not merely expressing sedation, otherwise the observed subjective sedation would have resulted in analgesia. This is an important finding for future studies to benchmark the effects of novel analgesics that may demonstrate a degree of sedation, including subtype selective GABA_A agonists or novel mixed MOP/NOP receptor agonists.

At first glance, it may have been surprising that the battery of evoked pain tasks was not sensitive to

Table 3 Summary of LSM analyses for subjective cognitive functioning and psychotomimetic symptoms.

	Placebo (n = 24)		Paracetamol (n = 23)		Promethazine (n = 23)		Δ9-THC (n = 24)	
	LSMean (95%CI)	Contrast vs. placebo ^a (95%CI)	LSMean (95%CI)	Contrast vs. placebo ^a (95%CI)	LSMean (95%CI)	Contrast vs. placebo (95%CI)	LSMean (95%CI)	Contrast vs. placebo (95%CI)
VAS Bond and Lader								
Alertness (mm)	49.7 (48.7–50.7)	0.07 (–1.55, 1.68) <i>p</i> = 0.9339	49.8 (48.8–50.8)	0.07 (–1.55, 1.68)	47.2 (46.2–48.2)	–3.11 (–4.75, –1.48) <i>p</i> = 0.0002	45.7 (44.7–46.7)	–5.83 (–7.45, –4.21) <i>p</i> = <0.0001
Calmness (mm)	51.6 (50.6–52.6)	–0.73 (–2.57, 1.12) <i>p</i> = 0.4369	51.1 (50–52.1)	–0.73 (–2.57, 1.12)	51.9 (50.9–53)	0.46 (–1.38, 2.30) <i>p</i> = 0.6236	53.6 (52.6–54.7)	3.97 (2.11, 5.82) <i>p</i> = <0.0001
Mood (mm)	50.4 (49.7–51.1)	–0.42 (–1.39, 0.55) <i>p</i> = 0.3914	50.2 (49.5–50.9)	–0.42 (–1.39, 0.55)	50.7 (50–51.4)	0.10 (–0.88, 1.07) <i>p</i> = 0.8408	51 (50.3–51.6)	0.76 (–0.21, 1.74) <i>p</i> = 0.1244
VAS Bowdle								
Feeling high (LOGmm)	0.33 (0.28–0.39)	–0.0295 (–0.1347, 0.0757) <i>p</i> = 0.5804	0.31 (0.26–0.37)	–0.0295 (–0.1347, 0.0757)	0.35 (0.29–0.4)	0.0189 (–0.0859, 0.1237) <i>p</i> = 0.7225	0.71 (0.65–0.77)	0.7232 (0.6164, 0.8300) <i>p</i> = <0.0001
Internal perception (LOGmm)	0.32 (0.29–0.34)	–0.0061 (–0.0470, 0.0348) <i>p</i> = 0.7677	0.31 (0.29–0.34)	–0.0061 (–0.0470, 0.0348)	0.33 (0.31–0.35)	0.0269 (–0.0139, 0.0678) <i>p</i> = 0.1951	0.4 (0.38–0.42)	0.1705 (0.1292, 0.2117) <i>p</i> = <0.0001
External perception (LOGmm)	0.33 (0.28–0.37)	–0.0143 (–0.0957, 0.0670) <i>p</i> = 0.7279	0.32 (0.27–0.36)	–0.0143 (–0.0957, 0.0670)	0.34 (0.29–0.39)	0.0148 (–0.0664, 0.0960) <i>p</i> = 0.7189	0.55 (0.5–0.59)	0.4289 (0.3466, 0.5112) <i>p</i> = <0.0001

VAS, visual analogue scale.

^aContrasts over 0–4 h post dose.

Bold values signify that the *p*-value <0.05

detect analgesic effects of paracetamol over a period of 4 h postdose, as it is among the most widely used analgesics worldwide. It has been shown to be effective in the treatment of different types of clinical pain, although not all. While it is effective at reducing postoperative pain (Weil et al., 2007; McNicol et al., 2016), episodic tension headache (Stephens et al., 2016) and acute migraine (Derry et al., 2010), there is no evidence for its effectiveness in treating lower back pain (Williams et al., 2014; Saragiotto et al., 2016) or pain related to osteoarthritis (Machado et al., 2015). However, when looking at available literature on human evoked pain tasks in healthy volunteers, the image becomes more diffuse. For each of the pain tasks that were investigated in more than one clinical trial, positive as well as negative results have been reported: mixed results were obtained using the cold pressor (Yuan et al., 1998; Munsterhjelm et al., 2005; Miner, 2009; Tiippana et al., 2013), there was a single negative study for contact heat (Tiippana et al., 2013), and again mixed results for electrical pain (Olesen et al., 2007; Filitz et al., 2008; Bandschapp et al., 2011; Tiippana et al., 2013), mixed results for pressure pain (Romundstad et al., 2006; Olesen et al., 2007; Pickering et al., 2008) and only a single study showing analgesic effects on inflammatory pain using the UVB model (Ortner et al., 2012). Interestingly, the published studies measuring pain experience (post-test NRS or post-test VAS) tend to be more likely to show analgesia by paracetamol than studies measuring the more objective pain thresholds. This may indicate that paracetamol exerts its analgesic effect on the aspect of subjective pain experience by means of pain modulation rather than exerting changes in nociceptive pain perception thresholds. This differential effect was not observed in the present study. Additionally, the analgesic effects of paracetamol in human evoked pain models tend to be more subtle than the effect sizes that were used for the power calculation; therefore, the study may have been underpowered. This applies specifically to for the cold pressor task, where a nonsignificant increase in pain thresholds was observed. Summarizing, based on the findings in literature and the aforementioned hypothesis, the outcome might have been different if a two-way crossover compared to placebo design was used in which different endpoints, that is Laser Evoked Potentials (Arendt-Nielsen et al., 1991; Nielsen et al., 1991, 1992), were investigated.

Medicinal use of cannabis dates back tens of thousands of years (Abel, 1980). In the last decade, the role for (plant-derived or synthetic) cannabinoids

has shifted from complementary medicine to regular care for pain related to oncology (Abrams, 2016) and neuropathic pain resulting to spinal cord injury (Wilsey et al., 2016) or Multiple Sclerosis (MS) (Turcotte et al., 2015; Russo et al., 2016). The oral formulation of $\Delta 9$ -THC (Namisol[®]) that was used in the current study has been shown to be effective in reducing neuropathic pain in a recently performed study in 24 patients suffering from progressive MS after 4 weeks of chronic treatment (van Amerongen et al., 2017). However, given its interaction with the endocannabinoid system, it cannot be considered an 'antinociceptive' analgesic, even if it may have analgesic effects in some conditions. This is reflected in the results of clinical studies using human evoked pain models to investigate pharmacology and mechanism of action. Only two studies investigating the effects of either inhaled cannabis or oral $\Delta 9$ -THC showed a statistically significant reduction in pain sensation on the cold pressor task (Cooper et al., 2013) or the heat pain task (Greenwald and Stitzer, 2000). Two other studies investigating the effects on heat pain alone did not demonstrate this improvement (Roberts et al., 2006; Redmond et al., 2008). The results of the present study are in line with the results of Naef et al. (2003) and Kraft et al. (2008), who showed lack of analgesia on a set of pain tasks and even a significant or nonsignificant increase in pain sensation for electrical pain and cold pressor. The finding of $\Delta 9$ -THC induced hyperalgesia has also been observed in the clinic (Beaulieu, 2006). A possible explanation is that this effect is dose-related, due to a bell-shaped effect curve. As proposed by Walter et al. (2015), this narrow therapeutic window may be the result of co-activation of TRPA1 and TRPV1 channels along with CB1 receptors by $\Delta 9$ -THC at higher concentrations. The dose of 10 mg of the oral formulation of $\Delta 9$ -THC was the highest single dose that is administered to healthy volunteers of this formulation to date (Klumpers et al., 2012). Due to inter-subject variability, this dose may have been too high for some, as in four subjects, pharmacodynamic assessments were delayed or omitted as a result of adverse events associated with subjective effects and nausea. However, on a group level, only a reasonable reduction in subjective alertness was reported. Furthermore, a post hoc analysis excluding the measurements that may have been affected by AE's of moderate intensity did not lead to a different interpretation of the results compared to the intention-to-treat (ITT) analysis. Therefore, the ITT analysis was maintained and reported here. On the other hand, it is known that chronic and even acute

exposure to Δ 9-THC can induce a 'transient amotivational state' (Lawn et al., 2016), which may be misinterpreted as an apparent hyperalgesic state. This hyperalgesic state is in fact the result of the psychotropic effect profile of Δ 9-THC, as subjects become less motivated to complete the pain tasks. Despite our efforts, human evoked pain tasks remain also sensitive to the affective components of pain sensation, and thus susceptible to detect changes in motivation as well as pure analgesia.

Over the recent years, some evidence has gathered for the effectiveness of antihistaminergic drugs as adjuvant in the treatment of various pain states (Friedman et al., 2013, 2016; Behrbalk et al., 2014). However, there is no evidence for any acute analgesic effect in humans. As such, promethazine (50 mg) was selected as a negative control for Δ 9-THC and to investigate the effects of sedation on the battery of evoked pain tasks. In addition to an increased sensitivity for electrical and pressure pain, a decreased pain detection threshold for inflammatory pain was observed. Even though histamine is involved in the initial phase of erythema development, this role is not prominent in the delayed erythemic response (Woodward and Owen, 1982) and as such administration 24 h after UVB exposure is not likely to have influenced the pathophysiology of the UVB-induced erythema. Thus, the results of promethazine treatment may indicate a reduction of pain endurance, which could result from reduced motivation associated with sedative effects (expressed as a reduction in subjective alertness), rather than suppositious analgesia resulting from delayed or impaired responsiveness.

The present study adds to a body of research studies in which this exact battery of evoked pain tasks was used to investigate various analgesic compounds alone (Okkerse et al., 2016b,c,d) or combined (Okkerse et al., 2016a). As such, the battery of evoked pain tasks is pharmacologically validated for the effects of cannabinoids and sedatives. The battery of evoked pain tasks was not sensitive to detect analgesic effects of paracetamol, but that finding by itself provides information on the much debated and yet unrevealed pharmacological mechanism of action, as we are able to compare the results to other compounds with known mechanism of action. As recognized before (Lotsch et al., 2014, 2016; van Amerongen et al., 2016), translatability of findings from human evoked pain models to clinical pain remains elusive. Nonetheless, if used prudently, this battery of pain tasks can provide invaluable information on pharmacodynamic and pharmacokinetic

relationships in the early phases of drug development, especially when combined with other neurocognitive assessments.

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Author contributions

G. van Amerongen, P Siebenga, M L de Kam, G J Groeneveld and J L Hay involved in conception or design of the work. G van Amerongen and P Siebenga collected the data. G van Amerongen, P Siebenga, M L de Kam, G J Groeneveld and J L Hay analysed and interpreted the data. G van Amerongen drafted the article. P Siebenga, M L de Kam, G J Groeneveld and J L Hay involved in critical revision of the article. G van Amerongen, P Siebenga, M L de Kam, G J Groeneveld and J L Hay involved in final approval to be published.

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