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ORIGINAL RESEARCH ARTICLE

Pharmacokinetic/Pharmacodynamic Modeling of the Acute Heart Rate Effects of Delta-9 Tetrahydrocannabinol and Its Major Metabolites After Intravenous Injection in Healthy Volunteers

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Abstract

Background and Objectives Cannabis consumption is increasing in both the recreational and medical settings. Tetrahydrocannabinol (THC) is known to produce cardiovascular effects, but the specific roles of THC and its metabolites THC-OH and THC-COOH in cannabinoid-induced cardiovascular effects remain unclear. We hypothesized that THC and THC-OH mediate a cannabinoid-induced increase in heart rate in either an additive or synergistic fashion.

Methods The present study uses prospectively obtained data to evaluate the effect of THC and its metabolites on heart rate in healthy volunteers through non-linear mixed-effect pharmacokinetic/pharmacodynamic (PK/PD) modeling.

Results The PK/PD models reveal that THC, THC-OH and a combination of THC and THC-OH, but not THC-COOH, are responsible for THC-induced tachycardia. The EC50 of the THC Emax model was 0.53 µM, 25-fold the EC50 for the THC-OH Emax model. The General Empiric Dynamic Model indicates that THC and THC-OH act synergistically to increase heart rate. Neither sex nor CYP2C9 polymorphism contributes to THC-induced tachycardia.

Conclusion THC-OH but not THC-COOH contributes to the heart rate effect of THC and THC-OH may be acting in a synergistic manner with THC. This contributes to understanding the cardiovascular effects of THC and cannabis-induced cardiovascular events. Future research including further hemodynamic data will allow a detailed systems pharmacology or response surface model approach.

Trial registration www.isrctn.com; registration number ISRCTN53019164.

Key Points

The specific roles of THC and its metabolites THC-OH and THC-COOH in cannabinoid-induced effects on heart rate remain unclear.

The present study used prospectively obtained data from healthy volunteers to evaluate the effect of THC and its metabolites on heart rate.

Non-linear mixed-effect pharmacokinetic/pharmacodynamic (PK/PD) modeling revealed that THC and THC-OH, but not THC-COOH, are responsible for THC-induced increased heart rate and that THC and THC-OH act synergistically. Neither sex nor CYP2C9 polymorphisms contribute to THC-induced tachycardia.

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1 Introduction

Cannabis consumption is increasing in both the recreational and medical settings, and many countries and US states have decriminalized or legalized the medical and recreational use of cannabinoids or are debating legalization.

Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive constituent of cannabis. Metabolism to its principal active metabolite, 11-hydroxy-THC (THC-OH), and to its terminal metabolite, carboxy-tetrahydrocannabinol (THC-COOH), is CYP2C9-dependent. Pharmacokinetics and pharmacodynamics have been previously described [1]. CYP2C9 is polymorphic with *3 expressors producing less THC-COOH than wildtype carriers [2].

THC is known to produce cardiovascular effects such as an increase in heart rate (HR) [3–6]. Cannabis use has also been associated with development of coronary artery disease [7–9] and with cases of acute myocardial infarction in young adults and in patients with existing cardiac disease [10, 11]. The adjusted odds ratio for the association of daily cannabis use and coronary artery disease, myocardial infarction, stroke and the composite outcome (coronary heart disease, myocardial infarction and stroke) in US adults aged 18–74 years was 1.16 (95% CI 0.98–1.38), 1.25 (95% CI 1.07–1.46), 1.42 (95% CI 1.20–1.68) and 1.28 (95% CI 1.13–1.44), respectively [12]. The AHA has issued statements cautioning that using cannabis can cause heart disease [13].

The observed physiologic effects have been reported not to directly correlate with THC plasma concentrations [14]. The primary active metabolite of THC, THC-OH, has been dismissed as a cause of the cardiovascular effects as its concentration following smoking or IV administration of THC is only one-tenth of the parent drug concentration [15]. Only two studies have investigated the effect of THC-OH. The first study dates from 1972 and demonstrated a significant increase in HR in male volunteers but did not model the data [16]. The second study provides the sole report of a pharmacodynamic model for THC-OH [17]. The terminal metabolite THC-COOH has been reported not to be psychoactive but has been associated with neuropathic pain relief [18]. It has not been investigated for cardiovascular effects.

The specific roles of THC, THC-OH and THC-COOH in cannabinoid-induced cardiovascular effects and events thus remain unclear. We hypothesize that THC and THC-OH, but not THC-COOH, mediate the cannabinoid-induced increased HR in humans in either an additive or synergistic fashion.

The present study investigates the effects of THC, THC-OH and THC-COOH on HR through development of several population-based non-linear mixed-effect (NLME) pharmacokinetic/pharmacodynamic (PK/PD) models for THC and primary metabolites in healthy volunteers. We report several models along with a model selection process identifying the best model to predict cannabis-induced increased HR and an interpretation of the general pharmacodynamic drug interaction model where THC and THC-OH are fit simultaneously to explore synergy or antagonism. This contributes to understanding the cardiovascular effects of THC and cannabis-induced cardiovascular events.

2 Methods

This study is part of a larger project on the pharmacokinetics and effects of IV THC in healthy volunteers. We have previously used non-compartmental analysis (NCA), compartmental modeling (CM) and minimal physiologically based pharmacokinetic (mPBPK) modeling of THC and its metabolites in volunteers with known CYP2C9 status to detail THC disposition in humans [2].

The present study uses prospectively obtained data to evaluate the effect of THC, THC-OH and THC-COOH on heart rate in healthy volunteers through non-linear mixed-effect pharmacokinetic/pharmacodynamic (PK/PD) modeling.

2.1 Study Set-up

With ethics committee approval (Cantonal Ethics Committee Bern, Approval: KEK 241–09), permission of all relevant bodies (Federal Office of Public Health of the Swiss Confederation, Swissmedic) and written informed consent of all volunteers, 25 volunteers received a single dose of 0.1 mg/kg (3.18 μM/kg) THC intravenously in a controlled environment (recovery room of a university anesthesiology department). All volunteers had intravenous access as well as continuous monitoring of oxygen saturations, HR and arterial blood pressure. Inclusion criteria were age > 18 years and cannabis naïve or cannabis abstinent for at least 1 month. Exclusion criteria were pregnancy (negative test mandatory), tobacco smoking within the last 3 months, suspected ischemic heart disease, cardiac arrhythmias, body mass index (BMI) outside the range of 16–35 $kg*m^2$, hepatic P450 activity-altering medication, use of illicit drugs and treated or suspected psychiatric disease at any point during their lifetime. Genetic information for CYP2C9 polymorphisms was available for all volunteers. Details of the study set-up have been previously described [2].

2.2 Pharmacokinetic (PK) Data

Plasma concentrations of THC, THC-OH and THC-COOH were quantified by liquid chromatography with tandem mass spectrometry from blood samples drawn in short intervals (0, 1, 2, 5, 10, 15, 30, 45, 90, 180, 300 min; 11 sampling times) up to 5 h after a single IV bolus of THC and at 24 and 48 h. The limits of detection were 0.08 µg/l (0.2 nM) for THC, 0.2 µg/l (0.5 nM) for THC-OH and 1.4 µg/l (4.0 nM) for THC-COOH. The limits of quantification were 0.8 µg/l (2 nM) for THC, 0.5 µg/l (1 nM) for THC-OH and 2.0 µg/l (6 nM) for THC-COOH [2]. Measured plasma concentrations of THC and its metabolites were converted into molar concentrations using the following values: THC 314.46 g/mol, THC-OH 330.46 g/mol, THC-COOH 344.44 g/mol [2].

2.3 Pharmacodynamic (PD) Data

PD data included heart rate measurements recorded before IV injection of THC and at minutes 1, 2, 5, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180 and 300 after injection (15 timepoints).

2.4 Data Analysis and Modeling

As the drug concentrations at the site of action cannot be directly measured, we used a PK/PD model-based approach to evaluate the relationship between the observed plasma or predicted effect-site concentrations and the observed physiologic effect (HR). THC/THC-OH/THC-COOH concentrations vs. time (PK) and HR (PD) data were fit to several nonlinear mixed effect (NLME) compartmental PK and linear, maximum effect (Emax) and the General Empiric Dynamic PD models with post hoc covariate assessment of sex and CYP2C9 phenotype. Compartmental PK models were based on the previous publication [2]. The pharmacokinetic modeling of THC has been extensively reviewed [1]. The three-compartment structural model (3CM) for THC is a bolus dose linear model parameterized with clearance (CL) via CYP2C9 and volume of distribution (Vd) linked to a two-compartment model for THC-OH and a one-compartment model for THC-COOH. The PK error model was multiplicative (Cobs * (1+C,epsilon). This PK model was built, and we then linked the PD model in using both simultaneous and sequential approaches [19]. We linked the following PD models: (1) single entity linear with two and three exponents; (2) single entity agonist Emax with and without effect compartments and sigmoid terms; (3) general empiric dynamic model (GEDM) for two drugs as described by Gabrielsson and Weiner [20]. The GEDM model can detect competitive and noncompetitive interaction, synergism and antagonism.

The error model for all PD models was additive (E,obs + E,ε(epsilon)). Data analysis was restricted to the first 5 h after injection as cardiovascular effects persist for 2–3 h [15]. We modeled HR as the change in HR as a fraction of the maximum HR (fHR) in each individual, resulting in a range from 0 to 1.

$$\text{fHRi,t} = \text{delta HRi,t}/\text{maximum delta HRi}, \quad (1)$$

where fHRi,t is the fractional increase in heart rate for individual *i* at time *t*, delta HRi is the change in the HR for individual *i* at time = *t*, and maximum delta Hri is the maximal change in HR for individual *i*. Fractional value of maximal heart rate can be considered the probability of achieving the maximal heart rate in a given individual. This was employed to account for the fact that THC effects probably involve multiple receptors with a statistical distribution of binding sensitivity that is more appropriately described with a probability-based analysis. The Hill equation and associated pharmacodynamic models that were employed can be viewed in a probabilistic framework [21].

Stepwise (forward and backward, alpha = 0.05) covariate search for sex and CYP2C9 phenotype were conducted. The PK/PD models were ranked by Akaike information criteria [22]. The best single entity and GEDM PK/PD models were internally validated with a Visual Predictive Check (VPC), conditional weighted residuals (CWRES) plots, and between-subject (η) and residual error (ε) shrinkage. Bias and precision were assessed with a general linear model (GLM) of predicted vs. observed fHR (intercept = bias and absolute average prediction value = precision). The GEDM model was bootstrapped ($n = 100$) to determine CV% and 90% confidence intervals of the model parameters. Data are presented as mean and standard deviation or as median and interquartile range or numbers and percentages. A probability of ≤ 0.05 was considered statistically significant. Data were analyzed using Phoenix NLME (Phoenix© NLME Certara L.P.) and NCSS 2022 [NCSS 2022 Statistical software (2022) NCSS, LLC. Kayesville, Utah, USA, ncss.com/software/ncss].

3 Results

Data of 25 volunteers receiving THC were available for analysis. Eleven volunteers receiving THC were male (44%) and 14 were female (56%). Age [median (IQR)] was 23 (21–25) years, height was 171 (167–182) cm, and weight was 65 (57–73) kg with a baseline heart rate (HR) of 76 (68–81) beats per minute. The maximal change in HR [bpm, median, (IQR)] was 68 (58–83). Three volunteers were homozygous

for CYP2C9*3 [2]. Data consisted of 275 plasma concentrations of THC, 275 plasma concentrations of THC-OH, 243 plasma concentrations of THC-COOH (PK) and 362 HR (PD).

3.1 Pharmacokinetic (PK) Model

The heart rate effect did not last longer than 5 h, and the PK model for the PK/PD model was started with truncated concentration time data at $t = 5$ h. It was noted that the truncated concentration vs. time data would not support the previously reported 3,3,3 compartment model. Systematic simplification of the model by eliminating compartments led to the final compartmental PK model of the previous paper [2]. The final three-compartment structural model (3CM) for THC restricted to 5-h data was a bolus dose linear model parameterized with clearance (CL) via CYP2C9 and volume of distribution (Vd) linked to a two-compartment model for THC-OH and a one-compartment model for THC-COOH. The only substantial changes in this 5-h version from the published model [2] that was based on 48 h of data were (1) a transit compartment to link THC-OH was added, (2) the peripheral THC compartments were much smaller as the extensive distribution phase of THC was not completed in 5 h, and (3) THC-OH has two compartments and THC-COOH has a single compartment. There was no relationship between THC-COOH and fHR, so the THC-COOH portion of the PK model was removed. Stepwise (forward and backward) covariate search for sex and CYP2C9 phenotype was conducted, but no significant covariates were found. The typical value of THC clearance (θCL,THC) in our population was 59.4 l/h, and the typical value of THC-OH clearance (θCL,THC-OH) was 223 l/h. Residual unexplained error for THC (THCε) was 0.16 μM, THC-OHε = 0.21 μM. AIC for the PK model was −2571. PK model parameters and diagnostics appear in Table 1 and Fig. 1. The only substantial changes in this 5-h version from the published model [2], which was based on 48 h of data, were (1) a transit compartment to link THC-OH was added and (2) the peripheral THC compartments were much smaller as the extensive distribution phase of THC was not completed in 5 h.

3.2 Pharmacodynamic Models

Table 2 lists the various PD models with model equations. During graphical data inspection, data revealed a counterclockwise hysteresis loop when HR was plotted against THC concentration (Fig. 2). Counterclockwise hysteresis implies the metabolite is more potent than the parent [23]. According to AIC criteria, the sequential modeling approach was found to be superior to the simultaneous approach for all PK/PD models tested. The best models for THC and THC-OH (1B1, 2B2) and the GEDM for THC and THC-OH combined are described in detail below. THC-COOH was not related to HR in any PK/PD model tested and will not be discussed further. Information for all other models can be found in the supplementary material.

3.2.1 Models for THC Alone (Table 2, Models 1A1, 1A2, 1A3, 1B1, 1B2)

The best model in this series of THC PK/PD models was 1B1, an Emax PD model with effect site for THC. Model parameters and diagnostics appear in Table 3. Figure 3 contains goodness of fit plots, CWRES and VPC plots of effect (fHR) vs. time and effect vs. drug concentration [THC]. The AIC for model 1B1 (−2415) was the lowest AIC of all models. Epsilon (ε) shrinkage (1.0) was the major problem with this model, making traditional model diagnostics unreliable so that only AIC, CWRES, prediction bias and precision

Table 1 Pharmacokinetic model

Parameter (units)	Estimate	CV%	95% CI		etaCV%	eta shrinkage
VcTHC (l)	5.2	10.0	4.2	6.3	0.6	< 1
V2THC (l)	14.9	11.2	11.6	18.2	< 1	0.91
V3THC (l)	37.6	10.4	29.9	45.3	9.8	0.36
CLd1THC (l/h)	43.7	5.9	38.7	48.8	< 1	0.51
CLd2THC (l/h)	16.3	22.6	9.0	23.5	19	0.08
CLTHC (l/h)	59.4	6.8	51.4	67.3	8.1	0.02
VcTHC-OH (l)	65.3	28.9	28.3	102	37	0.04
V2THC-OH (l)	222	19.8	135	308	< 1	0.91
CLdTHCOH (l/h)	208	32	77.5	340	26	0.2
k-transit THC-OH (l/h)	56.2	25.8	27.7	84.7	< 1	0.88
CLTHC-OH (l/h)	223	10.7	176	270	12	0.04
ε (SD)THC (μM)	0.16	6.0	0.14	0.18		
ε (SD)THC-OH (μM)	0.21	9.0	0.17	0.25		

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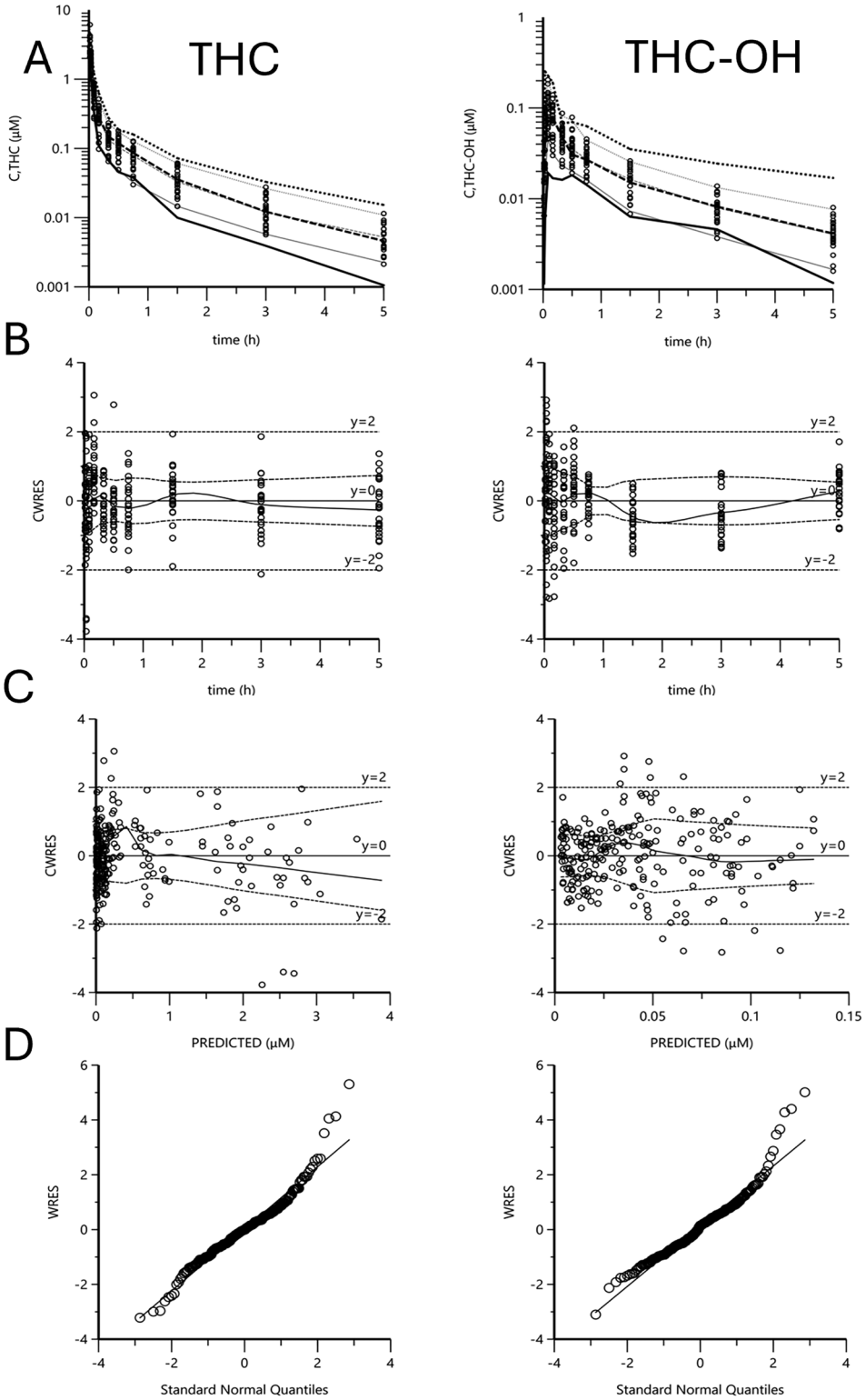

Fig. 1 Pharmacokinetic model diagnostic plots. **A** Visual predictive check for THC and THC-OH. The black lines indicate predicted and gray lines indicate observed means and 95% confidence intervals (CI). The dashed lines indicate the mean, the dotted lines indicate the upper 95% CI, and the solid lines indicate the lower 95% CI. Circles represent observed (dose/volume) THC concentrations. **B** Conditional weighted residual (CWRES) plots (Cobs-Cpred) vs. time for THC and THC-OH. **C** Conditional weighted residual (CWRES) plots (Cobs-Cpred) vs. observed concentrations of THC and THC-OH. **D** Quantile plots of weighted residuals

were used to validate this model [24]. CWRES vs. time and CWRES vs. predicted THC, fHR were within ± 2. GLM intercept for fHR was 0.1, and absolute average prediction error % (AAPE%) was 49.7% indicating a 10% positive bias and moderate precision. This model had robust estimates of the Emax parameters. CVs of the PD parameters were < 25%. The ke0 (effect compartment rate constant) of 6.2 l/h was equivalent to an effect site equilibration half-life of

Table 2 Pharmacodynamic model structure

Model no.	Agonist	Model equation
1A1	THC	fHR,THC = α + (β *Cthc)
1A2	THC	dCethc/dt = Ke0,thc * (Acthc - Cethc)
		fHR,THC = α + (β *Cethc)
1A3	THC	dCethc/dt = Ke0,thc * (Acthc - Cethc)
		fHR,THC = α + (β *Cethc) + (γ*Cethc^2)
1B1	THC	dCethc/dt = Ke0,thc * (Acthc - Cethc)
		fHR,THC = Emax,thc * Ce /(EC50,thc + Cethc)
1B2	THC	dCethc/dt = Ke0,thc * (Acthc - Cethc)
		fHR,THC = Emax,thc * Ce^{γ} /(EC50,thc^{γ} + $Cethc^{\gamma}$)
2A1	THC-OH	fHR,THC-OH = α + (β * Cthc-oh)
2A2	THC-OH	fHR,THC-OH = α + (β *Cthc-oh) + (γ*Cthc-oh^2)
2B1	THC-OH	fHR,THC-OH = Emax,thc-oh * C,thc-oh /(EC50thc-oh + C,thc-oh)
2B2	THC-OH	fHR,THC-OH = Emax,thc-oh * C,$thc\text{-}oh^{\gamma}$ /(EC50$thc\text{-}oh^{\gamma}$ + C,$thc\text{-}oh^{\gamma}$)
3GEDM	THC, THC-OH	fHR = Emaxthc*(Cethc/EC50thc + α * Cthc-oh/EC50OH + β * Cethc/EC50thc * Cthc-oh/EC50thc-oh / 1 + Cethc/EC50thc + δ * Cthc-oh/EC50thc-oh + γ * Cethc/EC50thc * Cthc-oh/EC50thc-oh)

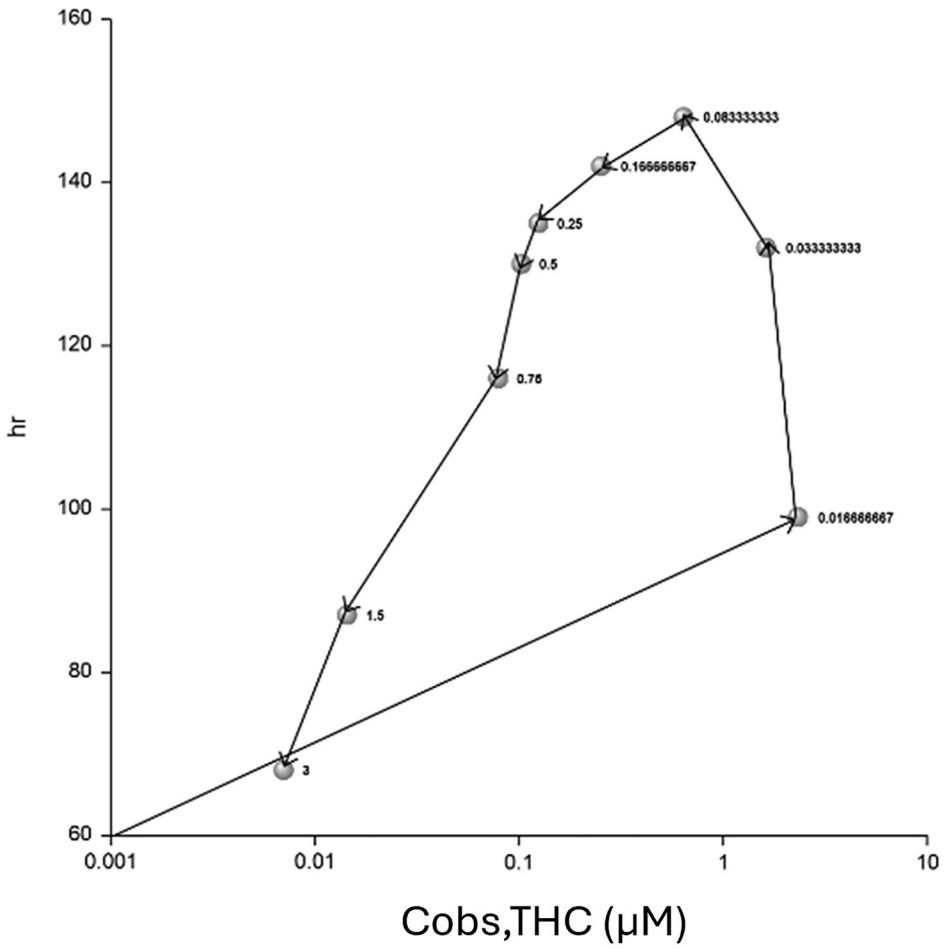

Fig. 2 Heart rate (hr) vs. observed concentration (C_{obs}) of THC for a typical subject, showing hysteresis. Arrows indicate the direction of time of the samples, with time of sample (in hours) noted beside each data point

Table 3 Model 1B1: THC alone, Emax with effect compartment

Parameter (units)	Value	%CV	95% CI		etaCV%	eta shrinkage
Ke0 (h)	6.22	16.1	4.3	8.2	16	0.46
EC50 (μM)	0.53	23.6	0.28	0.79	50	0.12
Emax (fHR)	0.96	3.8	0.89	1.03	< 1	0.94
ε (SD) THC (μM)	0.16	6.7	0.14	0.18		
ε (SD)THCOH (μM)	0.23	12.2	0.17	0.28		
ε (SD) fHR (fHR)	0.18	6.5	0.16	0.20		

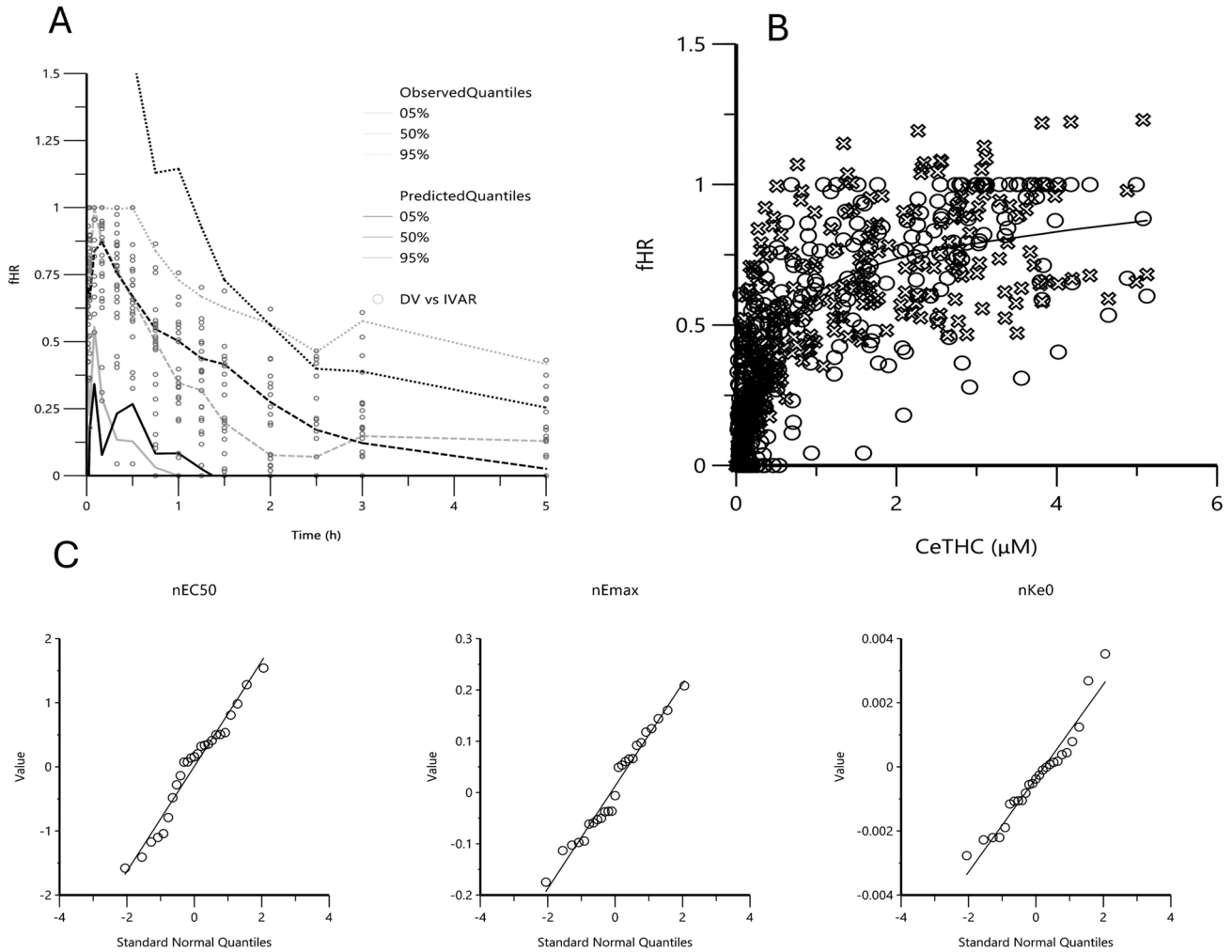

Fig. 3 PK/PD model 1B1 (THC alone): THC Emax diagnostic plots. **A** Visual predictive check. The black lines indicate predicted and gray lines indicate observed means and 95% confidence intervals of fractional heart rate (fHR). The dashed lines indicate the mean, the dotted lines indicate the upper 95% CI, and the solid lines indicate the lower 95% CI. Circles represent observed (DV) fHR. **B** Scatter plot of effect site THC vs. fHR with model (solid line). Circles are observed fHR. X are model-predicted fHR. **C** Quantile plots for between subject variability (η) of EC50, Emax and Ke0

0.12 h, or 7 min, which matches the onset of tachycardia in our data. The EC50 for THC was 0.53 μM, and Emax was 0.96. The between-subject variation (η CV%) in PD parameters for EC50 50% and η shrinkage was excessive, preventing reliable between-subject variability estimates of ke0 and Emax. The HR effect was well described by the model, as shown in the VPC in Fig. 1. However, the VPC may be incorrect because of the large ε and η shrinkage. No covariate was found significant in a stepwise covariate search including sex and CYP2C9 phenotype, subject to the η shrinkage. The raw, observed heart rate is plotted against THC concentration in Supplementary Fig. 1.

Table 4 Model 2B2: THC-OH alone, sigmoid Emax

Parameter (units)	Value	%CV	95% CI		eta CV%	eta shrinkage
EC50 (μM)	0.02	12.5	0.017	0.028	31	0.08
Emax (fHR)	0.91	4.6	0.82	0.99	< 1	0.97
Gamma	2.14	9.7	1.7	2.5	< 1	0.81
ε (SD) THC (μM)	0.16	6.8	0.14	0.18		
ε (SD) THC-OH (μM)	0.23	13.0	0.17	0.29		
ε (SD) fHR	0.18	5.0	0.16	0.20		

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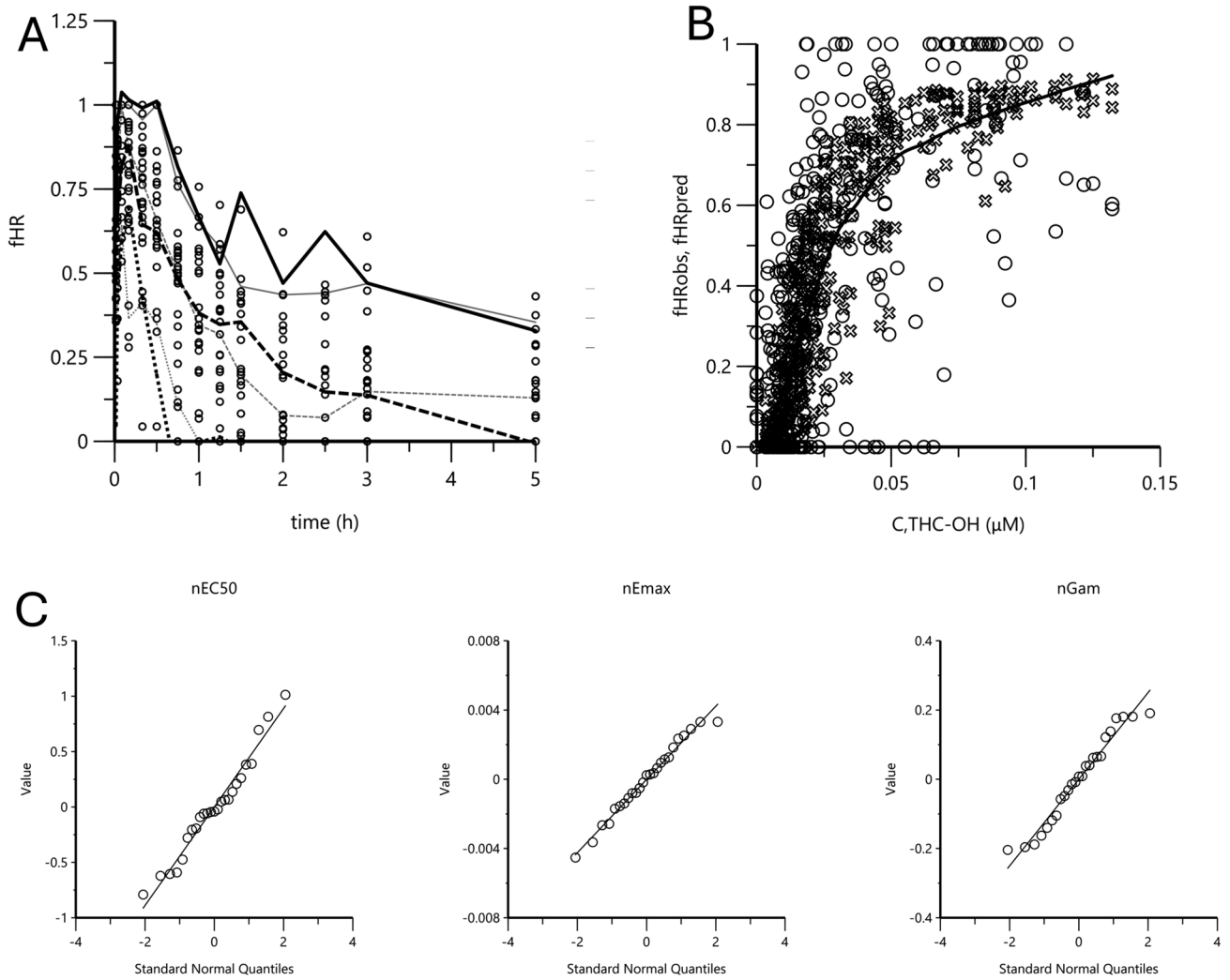

Fig. 4 PK/PD model 2B2 (THC-OH alone): THC-OH Emax diagnostic plots. **A** Visual predictive check. The black lines indicate predicted and gray lines indicate observed means and 95% confidence intervals of fractional heart rate (fHR). Circles represent observed (DV) fHR. **B** Scatter plot of effect site THC vs. fHR with model (solid line). Circles are observed fHR. X is model predicted fHR. **C** Quantile plots for between-subject variability (η) of EC50, Emax and nGamma (nGam)

3.2.2 Models for THC-OH Alone (Table 2, Models 2A1, 2A2, 2B1 and 2B2)

THC-OH alone PK/PD model 2B2 was the best of this series of models for THC-OH. Model parameters and diagnostics are shown in Table 4 and Fig. 4. Model 2B2 was a sigmoid Emax model for THC-OH without an effect site. The AIC was − 2378, the second-best AIC of all

models. The EC50 for THCOH was 0.02 µM, and gamma was 2.1. Eta (η) shrinkage was high for Emax (0.97) and gamma (0.81), preventing reliable between-subject variability estimates of these PD model parameters. Epsilon shrinkage was low at 0.05. The between-subject variation (η CV%) for EC50 was 31%. Despite excessive shrinkage, the model parameter typical estimates CVs for EC50, Emax and gamma were < 15%. GLM intercept was = 0.1; absolute average prediction error % (AAPE%) was 100%, indicating 10% positive bias and poor precision. The HR effect was well described by the model as shown in the VPC plot in Fig. 3. No covariate was found significant in a stepwise covariate search including sex and CYP2C9 phenotype, subject to η shrinkage. The raw observed heart rate is plotted against THC-OH concentration in Supplementary Fig. 2.

3.2.3 Combined Models: THC and THC-OH General Empirical Dynamic Model GEDM

Model 3GEDM is a combined model able to detect both competitive and non-competitive interactions and synergism or antagonism. Model parameters and diagnostics are given in Table 5 and Fig. 5. There are four model hyperparameters, α, β, δ and γ, in addition to EC50 and EA50. Effect site THC was the agonist and THC-OH was the antagonist or synergist. The model bootstrap parameters were not significantly different from the model fit parameters. Bootstrap

Table 5 Model 3A: THC and THC-OH GEDM: general empirical dynamic model

Parameter (units)	Value	Boot value	Boot %CV	Boot 95% CI		Boot eta CV%
Ke0 (l/h)	0.26	0.37	60	0.24	0.95	< 1
EC50 THC(µM)	1.24	1.44	18	1.0	2.0	200
EC50 THC-OH(µM)	0.12	0.13	10	0.1	0.15	< 1
Emax (fHR)	1 (fixed)	1 (fixed)				
α	0.74	0.74	8	0.62	0.84	1.1
β	0.94	0.93	10	0.74	1.12	5
δ	0.48	0.42	19	0.24	0.52	4
γ	0.50	0.44	28	0.25	0.54	< 1
ε (SD)THC (µM)	0.22	0.22	7.2	0.19	0.25	
ε (SD) THC-OH(µM)	0.21	0.21	6.3	0.18	0.23	
ε (SD) fHR		0.22	6.6	0.20	0.26	

AIC-2499; NOBS = 817

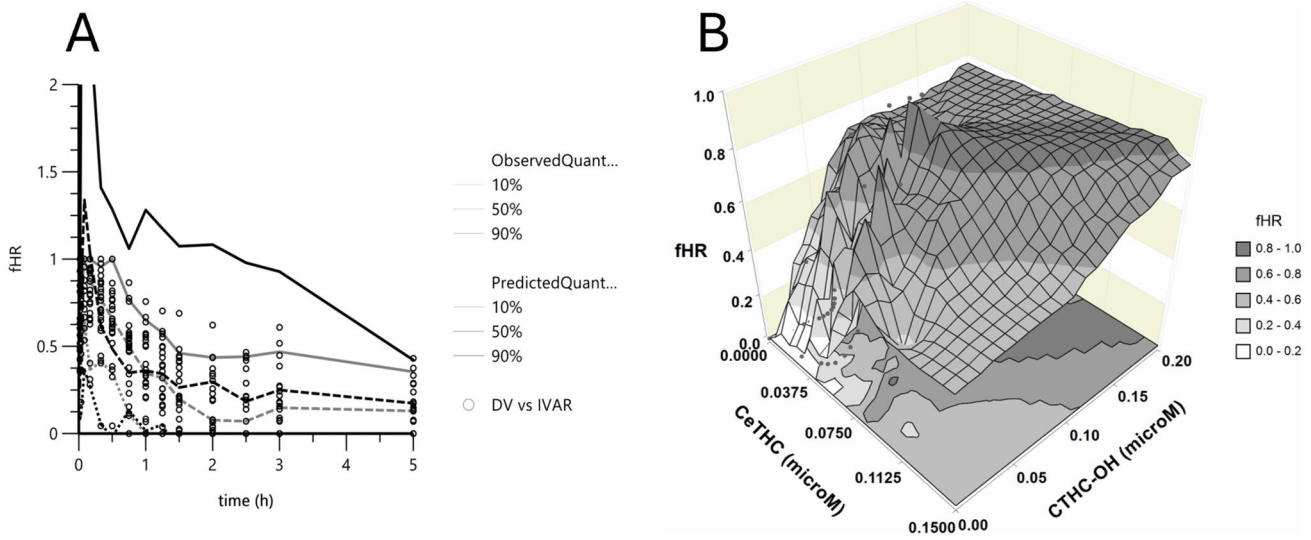

Fig. 5 PK/PD Model 3: Combined THC and THC-OH general empiric dynamic model (GEDM) diagnostic plots. **A** Visual predictive check. The black lines indicate predicted and gray lines indicate observed means and 95% confidence intervals of fractional heart rate (fHR). Circles represent observed (DV) fHR. **B** Three-dimensional surface plot of the GEDM model. The *x*-axis is predicted THC-OH, the *y*-axis is predicted THC, and the z-axis is predicted fHR. Circles are observed fHR

values were EC50,THC = 1.44 µM, EC50,THC-OH = 0.13 µM, α = 0.74, β = 0.93, δ = 0.42 and γ = 0.44. The AIC of model 3A was −2499; epsilon shrinkage was 0.18. The bootstrap parameter CV%s for α, β, δ and γ were 8, 10, 19 and 28, respectively; the bootstrap eta CV%s for α, β, δ and γ were 1.1, 5, 4 and 1, respectively. The model had a small positive bias (GLM intercept = 12%) and moderate precision (AAPE% = 36%). Table 6 is a reproduction of a table in Gabrielsson and Weiner [20]. This table lists criteria for interpretation of the model hyperparameters for declaring competitive or noncompetitive interaction, synergism or antagonism. We found that the model hyperparameters met criteria 4 and 5, indicating competitive or non-competitive synergism. The three-dimensional surface plot of this model is available in Fig. 5, which displays the synergistic effect of THC and THC-OH. Covariate analysis was conducted, but no significant covariates were found.

4 Discussion

This study used prospectively obtained pharmacokinetic and pharmacodynamic data from healthy volunteers who received an IV bolus of THC or placebo to delineate the effects of THC and its primary active metabolite, THC-OH, on HR in humans. Several non-linear mixed-effect (NLME) pharmacokinetic/pharmacodynamic (PK/PD) models for THC and THC-OH were established and tested. These data contribute to a better understanding of the cardiovascular effects of THC.

The PK/PD models indicate one could explain the variability in the THC-induced HR change with the parent THC (model 1B1) or the metabolite THC-OH (model 2B2) or a combination of the two (GEDM). THC-COOH was not related to the change in HR. The EC50 of the THC Emax model was 0.53 µM, 25-fold the EC50 (0.02 µM) for the THC-OH Emax model. The GEDM model indicates that THC and THC-OH act synergistically to increase heart rate. Sex did not contribute to the variability of HR. The CYP2C9 phenotype did not contribute to the HR effects observed as the polymorphism effect is seen in the PK of the terminal metabolite (THC-COOH) only.

Table 6 Summary of general empirical dynamic model criteria [20]

Criteria	β	α	Model
1	1 + α	1	Two separate Emax models
2	1	1	Noncompetitive interaction
3	0	0	Competitive interaction
4	0 < β < 1	β	Competitive and non-competitive
5	> δ	>0	Synergism
6	< δ	>0	Antagonism

The ideal way to define the contribution of THC and THC-OH to the cardiovascular effects of THC would be to investigate the effect of THC alone and the effect of THC-OH alone. Since to date the metabolism of THC to THC-OH cannot be blocked, this is not feasible, and any investigation of the pharmacodynamic effects of THC is confounded by the presence of THC-OH and THC-COOH. Previous investigations have neglected or minimized the effect of THC-OH by noting that the THC-OH concentration is only 1/10 of the concentration of the parent drug [15]. This logic ignores the possibility that the metabolite may be pharmacologically more potent than the parent drug and ignores synergism or antagonism. Our modeling results indicate THC-OH must be from 10- to 25-fold more potent than THC to achieve the change in heart rate seen in our volunteers; plots of HR vs. THC-OH show counterclockwise hysteresis supporting the PK/PD model result, and our GEDM results indicate synergy of THC and THC-OH [20, 23].

Other investigations used plant-derived cannabis rather than THC alone. Thus, the pharmacologic effect is a result of the entourage effect that includes cannabidiol (CBD), other cannabinoids and other substances that comprise the 500 compounds in *Cannabis sativa*, not to mention the product of combustion when the drug is smoked [25].

The presented data are derived from an IV injection of THC alone and thus are free from the confounding effect of the entourage of other substances. Also, although the oral and inhalational routes are more commonly used, the IV route was chosen to avoid issues of uncertain bioavailability of oral and inhalation routes. The employed method of PK/PD modeling provides an objective method to compare the ability of the various models to predict the observed HR changes.

At least three distinct pharmacologic mechanisms could potentially cause the HR effect of cannabis. The first is simple binding as an agonist at the beta-adrenergic receptor, the second is inhibition of the acetylcholine signal to the sinoatrial node decreasing vagal tone, and the third is binding to the CB1 receptor in the myocardium and increasing HR via the endocannabinoid system [8, 26, 27]. There is no evidence to support THC binding to the beta-adrenergic receptor, but beta blockers can mitigate the effect of cannabis-induced tachycardia [26]. Regarding the cholinergic nervous system, THC could inhibit acetylcholine binding at the sinoatrial node, causing increased HR. In fact, atropine has been shown to enhance the HR effect of THC [26]. Autonomic effects have recently been investigated by Nardone et al. in 22 habitual recreational cannabis users who found cannabis flower vaporization decreased cardiac baroreflex and heart rate variability [28].

Evidence for the cannabinoid mechanism suggests the receptor in question is CB1 [8]. Studies that report the binding of THC to CB1 note a Ki of 18 to 32 nM, or about 1/10

of the THCEC50 from model 1B1 of our data [29–31]. This Ki is a free concentration, and since THC is > 90% protein bound, the discrepancy is explained by the protein binding [2]. The free concentration EC50 for THC in our study is 53 nM. The ke0 of 6 l/h is equivalent to an effect site equilibration half-life of 0.12 h, or 7 min, which matches the onset of tachycardia in our volunteer data. There is evidence that CB1 exists in the myocardium, and it may be a receptor for anandamide or 2-AG regulating HR [32]. Several CB1 receptor antagonists can competitively reduce the tachycardic effect of THC [33]. CB1 receptor binding is complex; it is a presynaptic G-protein-coupled receptor (GPCR). Endogenous ligands anandamide and 2-arachidonylglycerol are either partial antagonists or inverse antagonists and use retrograde signaling [34]. The CB1 receptor is buried in the lipid bilayer, and access to the receptor binding site means the agonist must diffuse across the lipid membrane. This could be consistent with the production of the hysteresis loop noted in our study, which reconfirms findings from other reports [15]. Anandamide is also known to cause vasodilation and tachycardia may be a reflex mechanism to maintain cardiac output as systolic and diastolic blood pressure is not altered after THC [8]. Reflex tachycardia may also be an explanation for the HR attenuating effect of beta blockers seen in the Benowitz study [26].

A recent review of the literature of PK/PD modeling of cannabis commented on the complexity of the endocannabinoid system and claimed that because of the lack of specificity of ligand to receptor response and alterations that occur with disease, cannabinoid dose-response relationships may be relatively unpredictable [35].

Here, we summarize the results of related studies for comparison with the presented results: Strougo et al. modeled a concentration-effect relationship for THC using results from a two-way crossover study with 12 healthy male volunteers who were administered placebo or rising doses of THC compounded into an alcohol-based solution that was vaporized at 90-min intervals [15]. Results demonstrated a time delay (hysteresis) in observed effects compared with plasma concentrations of THC, but the author did not state the direction of the hysteresis. The baseline Emax model did not include THC-OH. Baseline effect E0 was 65.3 bpm, EC50 was 30.7 ng/ml (0.098 μM), and Emax was 41.5 bpm. Ke0 was 5.41 l/h, which is a t1/2 to the effect compartment of 7.7 min, similar to all THC models we report. The study concludes that the effect on HR was due to THC only and was mediated by CB1 in human atrial tissue. Although not reported in numeric form, using the graphical data we can infer the THC Cmax in the Strougo study was 100 ng/ml or 0.03 μM; THC-OH Cmax was 0.02 μM, almost 100-fold lower than that achieved in our study where the THC Cmax was 2.6 μM and the THC-OH Cmax was 0.1 μM. The Strougo study may have not reached a THC concentration sufficient to reach the maximum effect, which makes the Emax and EC50 estimates suspect [36]. A comparison of the EC50 from our study 0.57 μM to Strougo 0.098, and Emax 68 bpm vs. 41.5 further supports this hypothesis. No model shrinkage data were reported.

Guan et al. retrospectively reviewed the results of four CB1 antagonists in THC challenge tests in healthy volunteers [36]. THC was not from plant-based cannabis but was compounded into an alcohol-based solution that was vaporized. Population-based NLME Emax models for THC with an effect compartment and a term for a competitive antagonist were fit. Results for THC alone were EC50 0.23 μM (18% relative standard error) with Emax of 64 beats per minute; however, the maximum reported heart rate was 120. They observed dose-dependent reduction in THC-induced HR of 20% at 5 mg to 80% at 1000 mg for the CB1 antagonists drinabant, surinabant, rimonabant and TM38837. THC Cmax was 0.29 μM in the surinabant experiment [33]. The experiments with the four different CB1 antagonists reported by Guan et al. [33] may not have reached a THC concentration sufficient to reach the maximum effect, which makes the Emax and EC50 estimates suspect [36]. Also, THC-OH was not measured. As these drugs are selective CB1 antagonists, the experiments do lend substantial evidence to support the CB1 receptor pathway as the cause of THC-induced tachycardia.

Klumpers et al. [37] studied a tablet formulation of oral THC Namisol®. Healthy volunteers received 6.5 mg or 8.0 mg THC orally, and THC and THC-OH concentrations and HR were measured. They used population-based NLME modeling for compartmental PK and ANOVA for PD. THC Cmax was only 0.03 μM after the 8 mg tablet. Although no PD model was fit, they mention the HR effects matched the THC-OH concentration curve better than the THC curve.

Joerger et al. [17] fit an Emax model for HR to data from nine patients with amyotrophic lateral sclerosis who received single oral doses of THC 5 and 10 mg observed for 8 h. Model parameters were THC-OH EC50 = 3.2e − 4 μM, Emax = 93 bpm. The PD estimates of this model are again suspect because of failure to reach Emax because of low cannabinoid concentrations following oral exposure [36]. To our knowledge, this is the only report of a model for HR and THC-OH, and it found a substantially lower EC50 for THC-OH than we report (0.02 μM). Oral dosing with subsequent low plasma THC concentrations prevented Emax from being correctly assessed; they report an HR Emax of 93 bpm.

In summary, many of the PK/PD modeling attempts to date have suffered from one or more of the following issues: (1) plant-based cannabis confounding by the entourage effect [25]; (2) oral dosing route with low bioavailability or low doses preventing achievement of Emax [36]; (3) plasma concentrations were measured with methods with low precision and accuracy [38, 39], assuming THC and THC-OH have similar

pharmacologic targets and or neglected THC-OH completely (see above); (4) no pharmacodynamic modeling or lack of model diagnostic information (see above).

In the presented study, delta-9-THC was administered intravenously, mitigating issues 1 and 2; we used a modern LC/MS assay and pharmacodynamic modeling of the parent and metabolite separately and in a combined model with reported model diagnostic information.

4.1 Limitations

The exact pharmacologic mechanism of the HR increase cannot be identified by PK/PD modelling of HR alone even though our data support the hypothesis that the HR increase is CB receptor mediated. Most models for cardiovascular assessment are conducted using individual parameters as we did using HR alone [40]. This ignores the underlying physiologic relationship among HR, stroke volume and cardiac output, and cardiac output, systemic vascular resistance and mean arterial pressures. There are systems pharmacology models that incorporate these factors [41], but we had no recordings of parameters such as stroke volume or systemic vascular resistance.

Also, the confounding effect of neuropsychiatric effects must be considered as in some people THC causes anxiety, which can by itself cause tachycardia independent of directly THC-induced mechanisms.

Our sample included 25 volunteers only, and some negative findings, such as the negative search for significant covariates, might be related to insufficient power [42]. Also, our data were from a single intravenous dose, which does not consider effects at steady-state and does not include bioavailability restrictions. The PK/PD differences regarding gender have been studied for THC and THC-OH. No differences in the PK or PD profile for either THC or THC-OH between males and females were found [43]. The objectives of this analysis do not allow a detailed discussion of the endocannabinoid system, which was reviewed recently [35]. Anandamide or 2-AG concentrations were not measured and could have contributed to the large variability seen in the PD models. Also, models are complex and should not be seen as predictive. Interpretation of the results of this modeling exercise must consider the degree of eta and epsilon shrinkage, which is a common but unrecognized issue in PK/PD models. To address shrinkage, we used validation methods that are robust in the face of epsilon shrinkage and discounted the validity of covariate analysis when eta shrinkage was > 30% [24].

5 Conclusion

This study investigated the effects of THC and THC-OH on HR through development of several non-linear mixed-effect pharmacokinetic/pharmacodynamic models in healthy volunteers given an IV bolus of THC. Our results indicate that THC-OH cannot be disregarded as contributing to the HR effect of cannabis and that THC-OH may be acting in a synergistic manner with THC. Our results also indicate THC-COOH does not contribute to the HR effect of cannabis. Future research needs to collect further hemodynamic data such as stroke volume and systemic vascular resistance to allow a systems pharmacology approach or a response surface model. Endogenous cannabinoids anandamide and 2-AG should be included in the models. These models need to include and report model diagnostic and validation criteria. Future research will also benefit by further elucidation of the endocannabinoid system and the use of heart rate variability analysis to further probe the autonomic effects.

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Declarations

Competing Interests The authors declare no competing interests.

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Authors Contributions WW: Conceptualization, methodology, PK/PD modeling, writing—original draft; RG: Conceptualization, investigation, methodology, project administration, supervision, validation, writing—review & editing; LT: Conceptualization, funding acquisition, investigation, methodology; MKB: Conceptualization, investigation, methodology, validation, writing—original draft.

Ethical Approval This study was conducted with ethics committee approval (Cantonal Ethics Committee Bern, approval number KEK 241–09) and approval of the relevant authorities (Federal Office of Public Health of the Swiss Confederation, Swissmedic). It was registered at www.isrctn.com (registration number ISRCTN53019164). This study was part of a larger trial on pharmacokinetics of intravenous THC.

Informed Consent All volunteers gave written informed consent prior to enrollment.

Consent for publication All patients gave written informed consent to participate in the study. No identifiable clinical photo of a patient or identifiable patient data are included in the publication. Hence no consent for publication to publish their data is required from individual patients.

Data Availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request and with ethics committee approval and approval of the relevant authorities.

Code availability The code for the Phoenix pharmacokinetic pharmacodynamic model can be requested from the corresponding author upon reasonable request.

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