

Supplementary Material

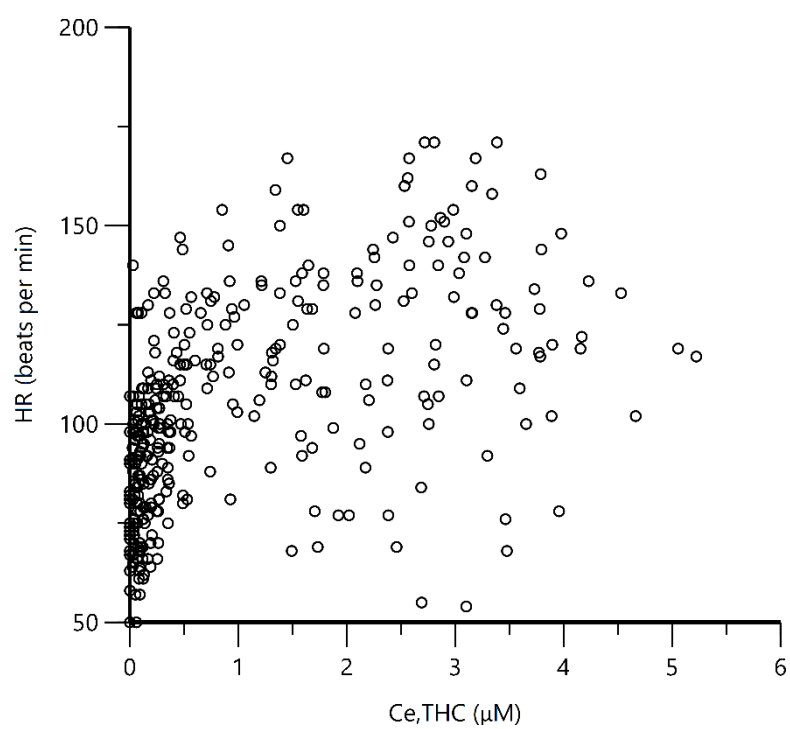
Manuscript title: Pharmacokinetic/ pharmacodynamic modeling of the acute heart rate effects of delta-9 tetrahydrocannabinol and its major metabolites after intravenous injection in healthy volunteers

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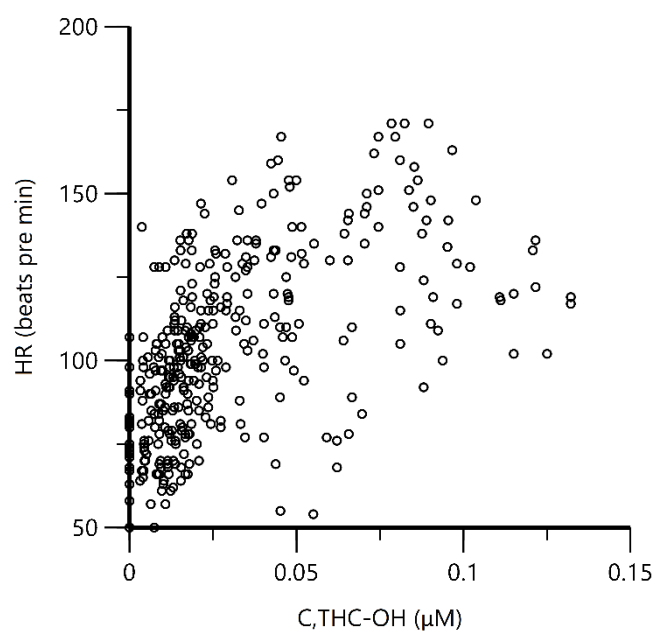
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Supplementary Figure 1 Observed heart rate (HR) vs THC concentration



Supplementary Figure 2 Observed heart rate (HR) vs THC-OH concentration



Rejected models

Model 1A2 THC linear with effect compartment

Parameter (units)	value	%CV	95% CI	etaCV%	eta shrinkage
Ke0 (1/h)	3.0	11.6	3.1-4.7	1.5	0.9
α (fHR)	0.16	29.5	0.05-0.16	40	0.26
β (fracBPM/ μ M)	1.7	12.0	0.42-0.68	0.8	0.34
Std dev THC (μ M)	0.16				
Std dev THC-OH (μ M)	0.23				
Std Dev HR (fBPM)	0.19				

AIC -22603; Condition # na; NOBS = 720; EPSILON shrinkage = 0.0541

THC alone PKPD model 1a2:

Model 1A3 THC 2nd order linear with effect compartment

Parameter (units)	value	%CV	95% CI	etaCV%	eta shrinkage
Ke0 (1/h)	4.3	11.6	3.1-4.7	1.5	0.9
α (fHR)	0.12	29.5	0.05-0.16	40	0.26
β (fracBPM/ μ M)	0.52	12.0	0.42-0.68	0.8	0.34
γ (fHR/ μ M ²)	-0.09	21.9	-0.15 - -0.07	0.1	0.94
Std dev THC (μ M)	0.19				
Std dev THC-OH (μ M)	0.22				
Std Dev HR (fBPM)	0.18				

AIC -1312; Condition # na; NOBS = 720; EPSILON shrinkage = 0.036

Model 2A2 THC-OH linear2

Parameter (units)	value	%CV	95% CI		etaCV%	eta shrinkage
α (fracBPM)	0.10	55	-0.007	0.20	60	0.25
β (fracBPM/ μ M)	14.7	10	11.7	17.7	<1	0.41
γ (fracBPM/ μ M ²)	-65	29	-28	-102	<1	0.94
stdevTHC (μ M)	0.16	6.2	0.14	0.18		
stdevTHCOH (μ M)	0.25	9.9	0.20	0.30		
stdevHR (fBPM)	0.20	7.3	0.17	0.23		

AIC -2578; Condition # = 2624; NOBS = 720; EPSILON shrinkage = 0.0518

Model 3 GEDM general empirical dynamic model for two drugs (simultaneous fit)

Parameter (units)	value	%CV	95% CI		eta CV%	eta shrinkage
Ke0 (1/h)	0.35	243	-1.3	2.0	<1	0.98
E _{max}	0.21	128390	-520	- 520	7.9	0.21
EC50 thc	0.31	128443	-790	790	42	0.44
EC50 thc-oh	0.03	34423	-20	20.8	<1	0.44
α	0.92	0.003	0.9168	0.9170	<1	0.97
β	0.68	0.003	0.6765	0.6766	<1	0.97
γ	0.66	394777	-5083	5084	<1	0.96
δ	0.46	247803	-2225	2226	<1	0.97
stddev0	0.25	12.6	0.19-0.31			
stdev1	0.23	18.7	0.15-0.31			
stdev2	0.23	17.8	0.15-0.32			

AIC -1831; Condition # = 4899179; NOBS = 720; EPSILON shrinkage = 0.1513

Model 1B2 THC Sigmoid Emax with effect compartment

Parameter (units)	value	%CV	95% CI		etaCV%	eta shrinkage
tvKe0 (h)	4.0	18.7	2.55	5.51	3	0.55
tvEC50 (μM)	1.78	31.5	0.67	2.9	10	0.65
tvEmax (fBPM)	1.48	18.8	0.95	2.01	<1	0.35
tvGamma	0.76	45	0.08	1.42		
stdevTHC (μM)	0.17	14.7	0.12	0.22		
stdevTHCOH (μM)	0.23	15.3	0.16	0.30		
stdevHR (fBPM)	0.17	9.3	0.14	0.20		

AIC -2127; Condition # = 2089; NOBS = 720; EPSILON shrinkage = 1.0

Model 2A1 THC-OH linear

Parameter (units)	value	%CV	95% CI		etaCV%	eta shrinkage
α (fracBPM)	0.19	31	0.07	0.31	23	0.29
β (fracBPM/μM)	8.2	14	6.0	10.5	9	0.24
stdevTHC (μM)	0.16	5.9	0.14	0.17		
stdevTHCOH (μM)	0.25	11.7	0.19	0.30		
stdevHR (fBPM)	0.21	6.4	0.18	0.23		

AIC -2550; Condition # = 2116; NOBS = 720; EPSILON shrinkage = 0.0651 MSE = -0.01 RMSE = 0.04

4 THC-OH competitive antagonist THC agonist inconsistent with GEDM results

Parameter	Estimate	CV%	2.5% CI	97.5% CI
tvKe0	5.3044311	36.123077	1.5422502	9.0666121
tvEmaxTHC	1.0079301	22.051792	0.57152437	1.4443358
tvEmaxOH	0.96892713	54.791232	-0.073434238	2.0112885
tvEA50OH	0.068062064	80.611125	-0.039662866	0.17578699
tvEC50THC	0.1948698	53.051738	-0.008113487	0.3978531

stdev0	0.22392205	7.2423531	0.19208061	0.25576349
stdev1	0.18549467	6.7223123	0.16101158	0.20997776
stdev2	0.22751877	11.958161	0.17409953	0.28093802

AIC -2564; Condition # = 11054; NOBS = 720; EPSILON shrinkage = 0.1671 MSE = -0.01 RMSE = 0.03