Pharmacokinetic/pharmacodynamic/pharmacogenomic(PK/PD/PG) non-linear mixed effect (NLME) modeling of the acute cardiovascular effects of delta-nine tetrahydrocannabinol (THC) and its major metabolite THC-OH after intravenous (IV) injection in healthy volunteers.

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BACKGROUND

- Cannabis (CB) causes increased heart rate (HR) in humans.(1) CB use disorder is associated with coronary artery disease (CAD).(2) The etiology of CB induced HR increase is unknown. Our hypothesis is that THC and 11-hydroxy THC (THC-OH) mediate increased HR via the cannabinoid receptor (CBR) in humans and depends upon the *2*3 polymorphism (PM) in CYP2C9.

OBJECTIVE

Our objectives are to identify: 1) the responsible moiety(s) and 2) CYP2C9 PM effects for CB increased HR.

METHODS

We fit NLME PK/PD/PG models to data from administration of 3.18 µM/kg IV THC in 25 volunteers.(3) Compartmental PK models were based on those published.(3) PD models included Emax with and without effect compartment (EC) and sigmoidicity (ɣ); and combined agonist/antagonist drug interaction models for THC and THC-OH. PD change in HR was parameterized as a fraction of the maximum change in HR (fMHR) from 0 to 1.

RESULTS

Data consisted of 455 plasma concentrations (PK) and 391 HR (PD).
Maximal change in HR (beats/minute, median, (IQR)) was 68(58-83) n=25, and 63 (54-66) for *2*3 PM n=3.
The PK/PG model θCLthc = 57.9 L/h with η of 11% was dependent on CYP2C9 PM. θCLthcoh = 197 L/h with η of 22%. Overall PK/PG model THCε = 0.16 µM, THC-OHε = 0.22 µM. AIC for the PK/PG model was -2564.

CONCLUSIONS

THC was responsible for CB HR increase based on the PK/PD/PG model with the lowest AIC. However, the combined models and the THC-OH alone model suggest THC-OH may also play a role given previous work with pre-formed THC-OH.(4) The *2*3 PM is related to HR response through PK metabolic CYP2C9 CL. Results may be useful for risk assessment of CB related CAD. Further research with pharmacodynamic response surface methodology is in process.

REFERENCES

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3) Wolowich WR, Greif R, Kleine-Brueggeney M, et al. Minimal Physiologically Based Pharmacokinetic Model of Intravenously and Orally Administered Delta-9-Tetrahydrocannabinol in Healthy Volunteers. Eur J Drug Metab Pharmacokinet. 2019 Oct;44(5):691-711.

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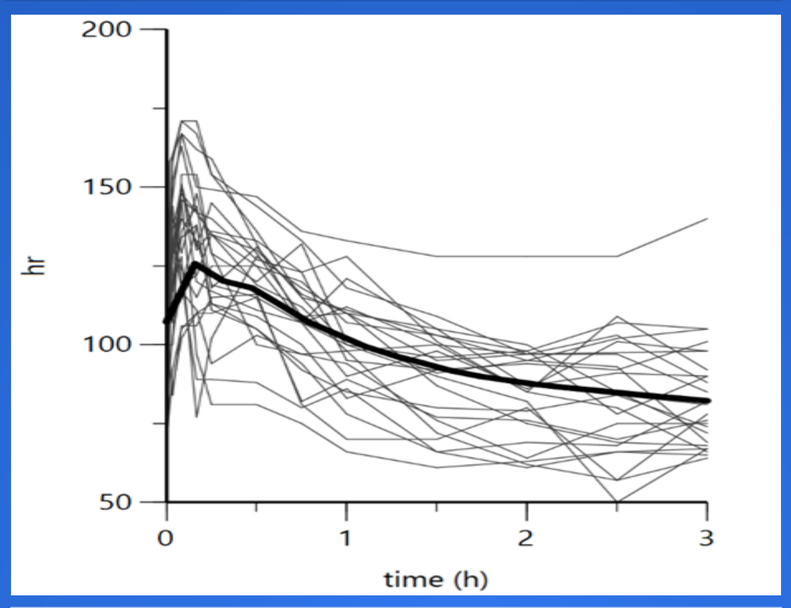
PK/PD/PG Model Parameters

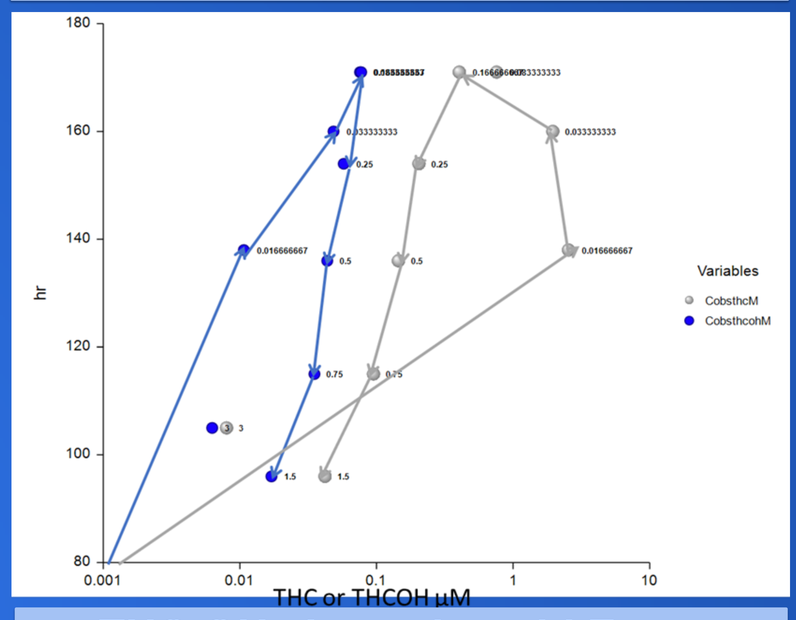
Model	THC alone Emax with effect cmpt				THC-OH alone sigmoidal Emax				Combined agonist				Competitive agonist (THC) / antagonist (THC-OH)			
parameter	θ	η%	η shrinkage	Ω	θ	η%	η shrinkage	Ω	θ	η%	η shrinkage	Ω	θ	η%	η shrinkage	Ω
EC_{50} (µM)	0.47	72%	0.12	0.55	0.02	33%	0.08	0.32	0.06	41%	0.13	0.45	1.03	113%	0.97	1.0^{-4}
Emax (fMHR)	0.94	12%	0.93	2.0^{-4}	0.90	26%	0.96	1.0^{-3}	0.99	14%	0.98	1.0^{-4}	0.73	22%	0.37	0.008
Ke0 (1/h)	5.97	57%	0.52	0.14												
ɣ					1.88	65%	0.69	0.03								
AIC	-2647				-2626				-2644				-2575			
EA50 (µM)													0.045	73%	0.10	0.33

Heart rate vs time

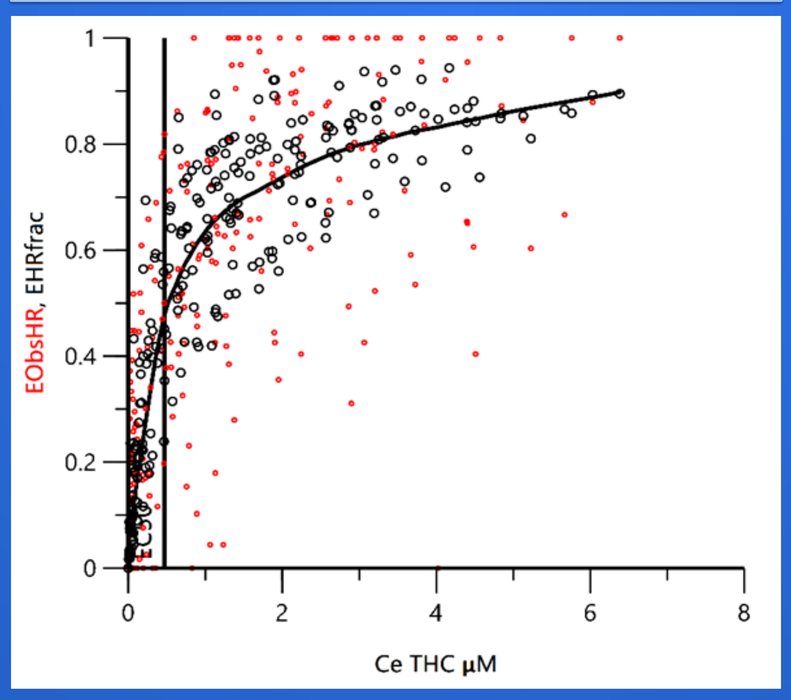


THC alone Emax with effect cmpt

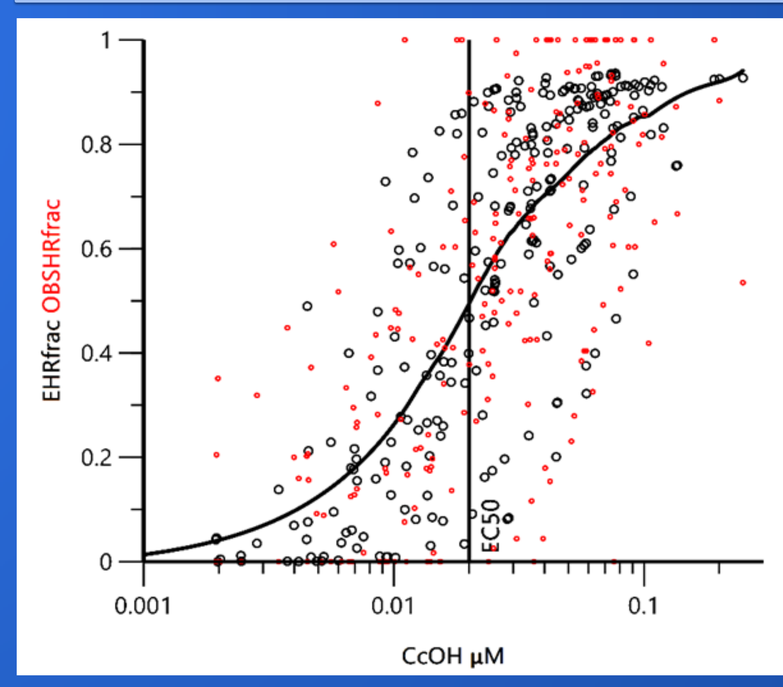
Hysteresis



THC-OH alone sigmoid Emax



THC THC-OH Combined agonist



THC Agonist THC-OH Competitive Antagonist