

A population pharmacokinetic model of dense delta-9-tetrahydrocannabinol (THC), 11-OH-THC, and THCCOOH data and its use to estimate daily exposure in an observational cannabis study with sparse data

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Objectives

- Develop a population PK model of THC¹, 11-OH-THC and THCCOOH from a Phase 1 clinical trial conducted at the National Institute of Drug Abuse (NIDA).
- Estimate daily consumption of THC from sparse data (plasma THC, 11-OH-THC, and THCCOOH plasma concentrations) in a cohort of regular cannabis users in Boulder, Colorado.

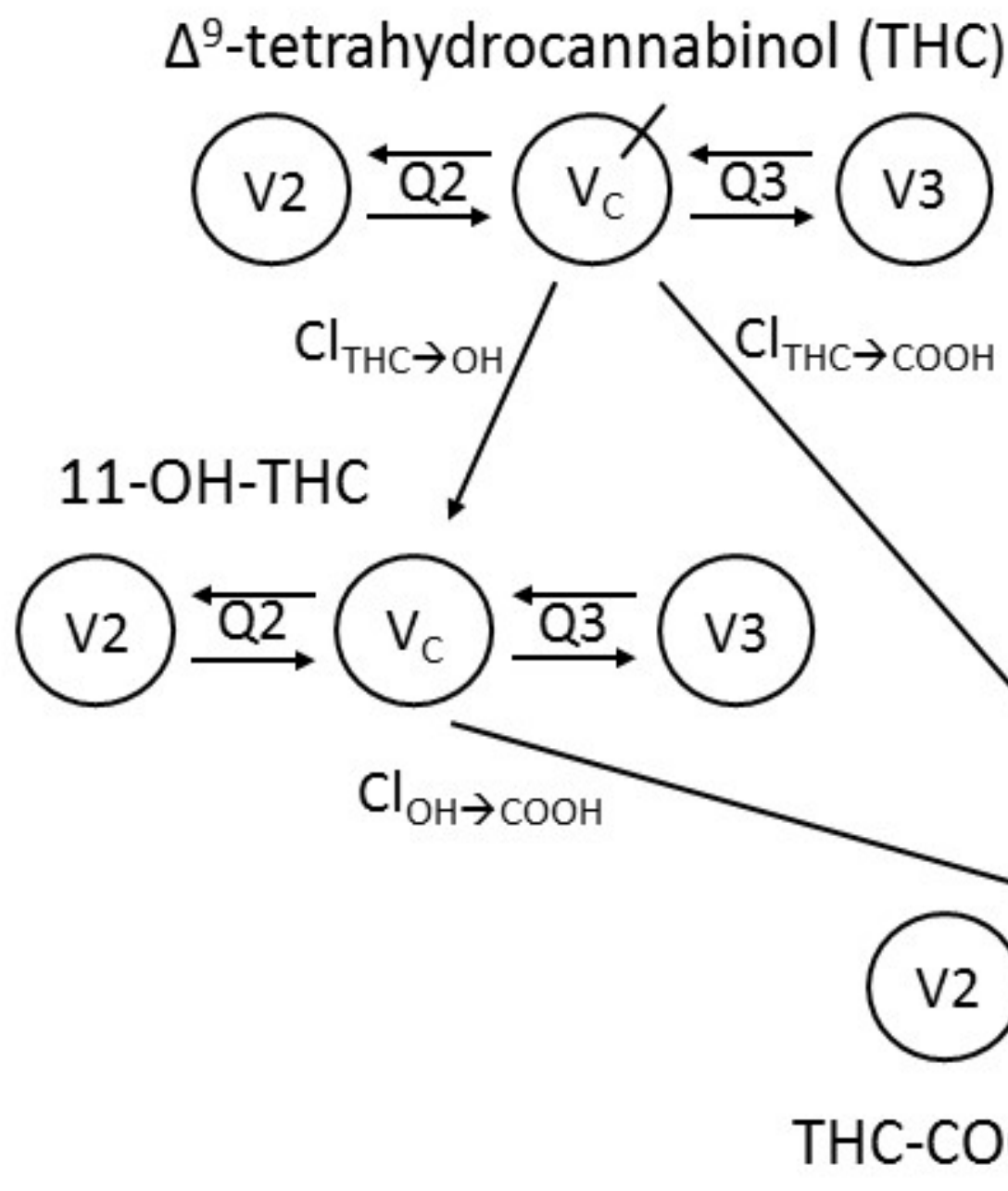
Methods

- At NIDA⁴, 6 sequestered subjects smoked in a rigorously-paced manner two different concentrations of marijuana cigarettes (1.75% and 3.55% THC) over 10 min one week apart.
- Frequent blood samples were obtained during and immediately after each smoking event and then less frequently for one week for the measurement of THC, 11-OH-THC and THCCOOH by GC-MS.⁴
- A multicompartment popPK model was developed using Phoenix NMLE 8.1.
- In Colorado, blood samples were obtained from 36 regular users of cannabis (16% or 24% THC by weight) at four time points:
 - Recruitment
 - in a mobile lab immediately before smoking in their home
 - upon returning to the mobile lab and then again one hour later
- THC and metabolites measured by LC-MS/MS⁵.
- The popPK of these data were analyzed with:
- distribution kinetics from the dense popPK analysis fixed to typical values
- clearances were modeled with the Bayesian prior (θ s and ω^2 s)
- Individual estimates for (1) daily THC consumption prior to recruitment, (2) daily THC consumption in the interval between recruitment and home-smoking, (3) the dose consumed during the home-smoking event and time at which smoking begun in home.
- Assumptions: steady-state for condition (1), one week between recruitment and study (2), last cannabis consumption at 10pm, in home smoking duration = 10 min

References

[1] Heuberger JA, et al., Clin Pharmacokinet 2015; 54: 209-219
[2] Karschner EL, et al., Clin Chem 2011; 57: 66-75
[3] Newmeyer MN, et al., Clin Chem 2016; 62: 1579-1592
[4] Huestis MA, et al., J Anal Toxicol, 1992; 16:276-282
[5] Klawitter J, et al., Ther Drug Monit, 2017; 39:556-564

THC/metabolite Model



Phase I Population PK Results

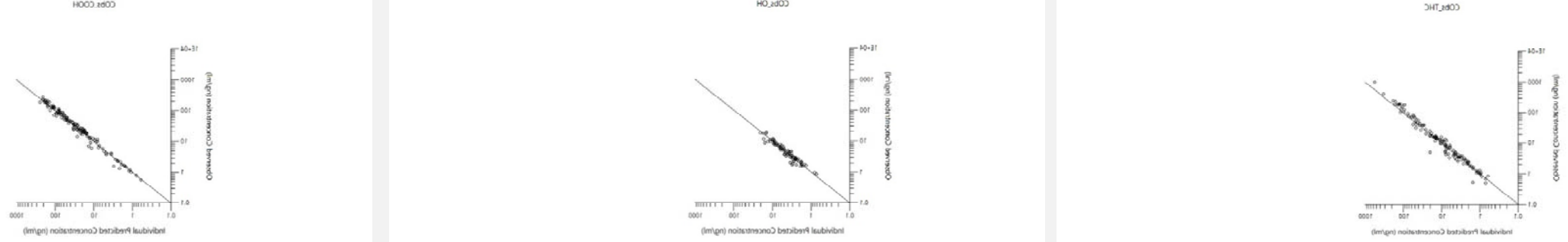
Table 2

		TYPICAL VALUE	±	SEE	ω^2	±	SEE
THC	VC (L)	28.5	±	3.77	0.09	±	0.04
	V2 (L)	45.6	±	5.61	5.16	±	3.06
	V3 (L)	3372	±	779	2.52	±	2.91
	Cl2 (L/min)	1.35	±	0.25	0.02	±	0.001
	Cl3 (L/min)	1.31	±	0.29	0.03	±	0.001
	Cle (L/min)	0.72	±	0.09	0.08	±	0.004
	f	0.89	±	0.12	0.02	±	0.001
	$\delta_{LowDose}$	0.23	±	0.03			
	$\delta_{HighDose}$	0.29	±	0.01			
	$\delta A_{LowDose}$ (ng/ml)	0.016	±	0.002			
	$\delta A_{HighDose}$ (ng/ml)	0.017	±	0.002			
11-OH-THC							
	Cl _{thc->oh} (L/min)	0.43	±	0.03	0.024	±	0.3
	VC (L)	34.4	±	7.56	0.2	±	0.15
	V2 (L)	15.7	±	5.7	*		
	V3 (L)	222.2	±	234.1	0.9	±	0.95
	Cl2 (L/min)	0.06	±	0.03	*		
	Cl3 (L/min)	6.58	±	0.57	1.35	±	1.38
	Cl _{oh->cooh} (L/min)	1.62	±	0.17	0.33	±	0.33
	$\delta_{LowDose}$	0.12	±	2.02			
	$\delta_{HighDose}$	0.08	±	0.04			
	$\delta A_{LowDose}$ (ng/ml)	2.14	±	0.99			
THCCOOH							
	Cle (L/min)	0.12	±	0.01	0.11	±	0.07
	$\delta_{LowDose}$	0.2	±	0.06			
	$\delta_{HighDose}$	0.32	±	0.05			
	$\delta A_{LowDose}$ (ng/ml)	0.58	±	0.17			
	$\delta A_{HighDose}$ (ng/ml)	0.39	±	0.14			

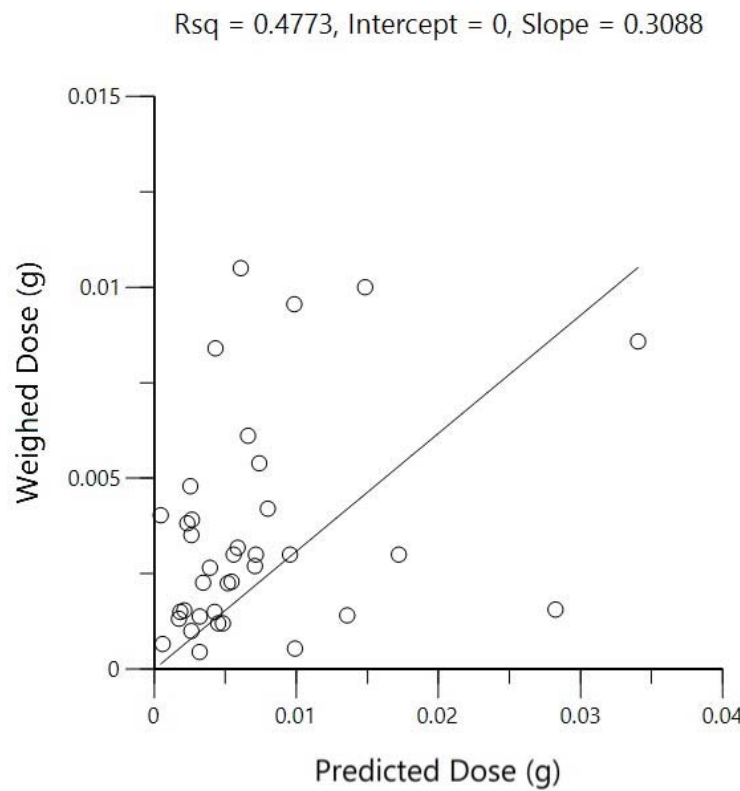
Observational Study Results

	TYPICAL VALUE	±	SEE	ω^2	±	SEE
THC						
CLE (L/MIN)	0.67	±	0.07			
11-OH-THC						
CL _{THC->OH} (L/MIN)	0.37	±	0.04			
CLOH->COOH (L/MIN)	1.13	±	0.39			
THCCOOH						
CLE (L/MIN)	0.10	±	0.02			
DOSES						
RECRUITMENT (MG/DAY)	16.8	±	12.2	1.68	±	0.97
INTERVAL (MG/DAY)	13.6	±	13.0	2.45	±	1.35
IN HOME/VAN (MG)	19.5	±	5.5	0.82	±	0.24

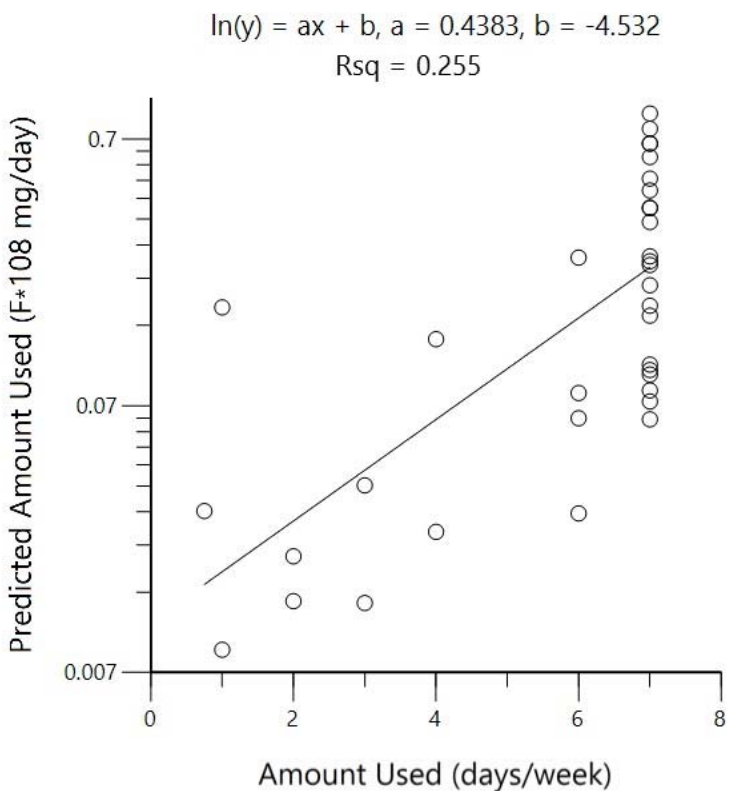
Observational Study Results: Figures



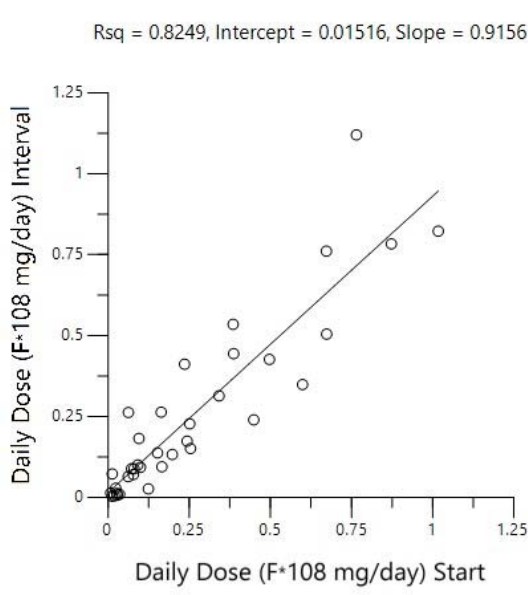
Diagnostic IPRED versus Observed



Weighed dose (cannabis taken to smoke in home – amount not smoked) versus model predicted



Stated cannabis usage pattern (days/week) versus estimated daily amount smoked



Estimated usage at Recruitment versus during Interval before Home Study

Conclusions

- Population PK model of THC and metabolites developed in Phase 1 study was able to estimate daily and single use THC consumption.
- Results suggest that users of cannabis with high THC content titrate their dosage
- ‘Efficiency’ of home smoking of cannabis with high THC content is approximately 1/3rd that of subjects smoking NIDA product (approx. 5% THC content) in a computer-paced manner.
- To analyze THC concentration data from blood samples obtained in an observational study with PK analyses, more detail of consumption pattern (e.g., time of last consumption, amount and times of daily use) should improve estimated daily dose.
- THC/metabolite concentrations and population PK may outperform usage questionnaires.