The Pharmacokinetics of Cannabis in Humans

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1

Disclosures

- Paid consultant to Zynerba Pharmaceuticals, Canopy Health Innovations, Battelle Memorial Institute, and Brain Solutions Inc.

2

Basics

- Cannabis is a botanical drug comprised of over 100 phytocannabinoids and over 400 other chemical substances (terpenoids and flavonoids)
- THC and CBD are primary phytocannabinoids and are of primary interest with respect to clinical effects
- Other minor cannabinoids and terpenoids are of interest, but little controlled research in humans has been completed on these compounds

3

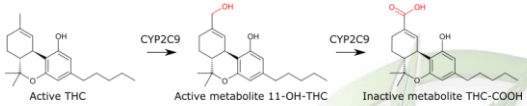
Cannabis is Unique

- Complex botanical drug
- Primary active constituents highly lipophilic
  - Non-linear half life; storage in adipose tissue
- Cannabis product types rapidly evolving
- Multiple routes of administration, formulations and chemotypes
- PK/PD relation is complicated

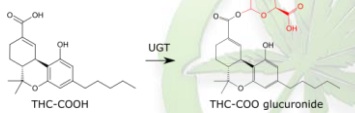
4

THC Metabolism

- **Oxidation**



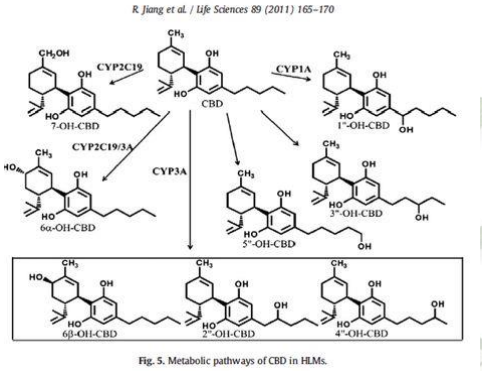
- **Glucuronidation**



- **Excretion**

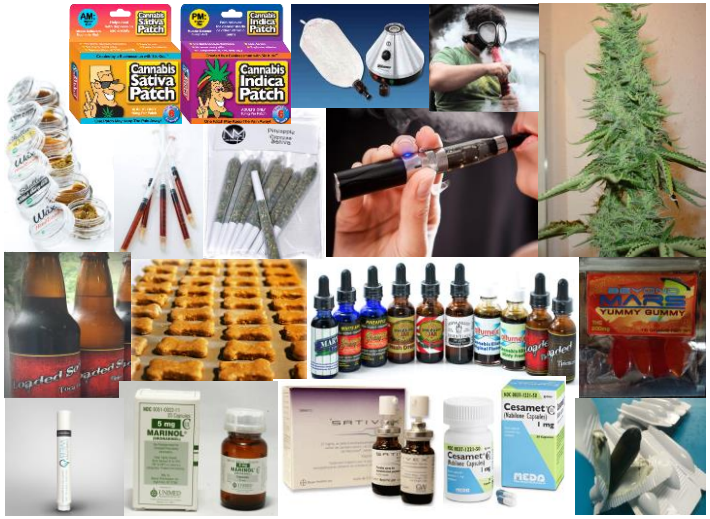
5

CBD Metabolism



See Review by Ujvary & Hanus, 2016

6



7

Key Questions

- **Impact of route of administration**
- **Passive exposure**
- **Variability across individuals**
- **Impact of formulation/chemotype**
- **Relation of blood cannabinoids to drug effects/impairment**

8

JHU Laboratory Research

- Funding from SAMHSA, NIH, and NIJ
- Controlled dosing in healthy adults
- Pharmacokinetic, subjective, cognitive and cardiovascular assessments
- Multiple routes of administration and doses
- Same protocol across studies
- Emphasis on non-tolerant, infrequent cannabis users
- Within-subject cross-over design

9

Following the Trailblazers

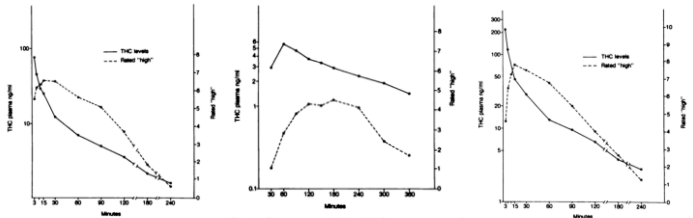


Fig. 4. Time course of "high" and relation to plasma concentration of THC following smoking of cannabis.

Fig. 6. Time course of "high" (lower curve) and relation to plasma concentration of THC (upper curve) following oral administration of THC.

Fig. 2. Time course of "high" and relation to plasma concentration of THC following intravenous administration of THC.

Hollister et al., 1981

10

Lindgren et al., 1981

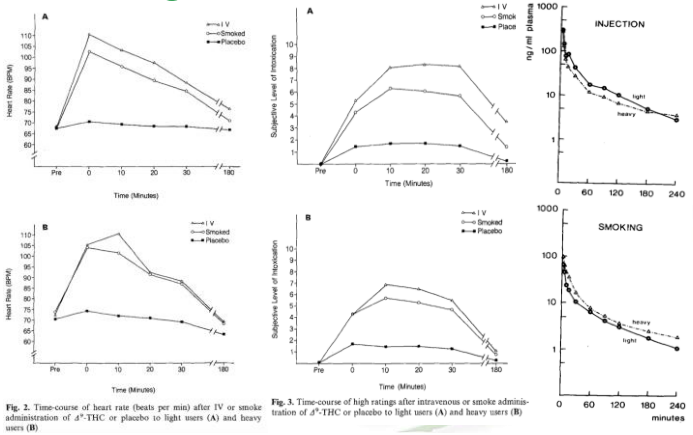


Fig. 2. Time-course of heart rate (beats per min) after IV or smoke administration of Δ^9-THC or placebo to light users (A) and heavy users (B)

Fig. 3. Time-course of high ratings after intravenous or smoke administration of Δ^9-THC or placebo to light users (A) and heavy users (B)

11

Abrams et al., 2007

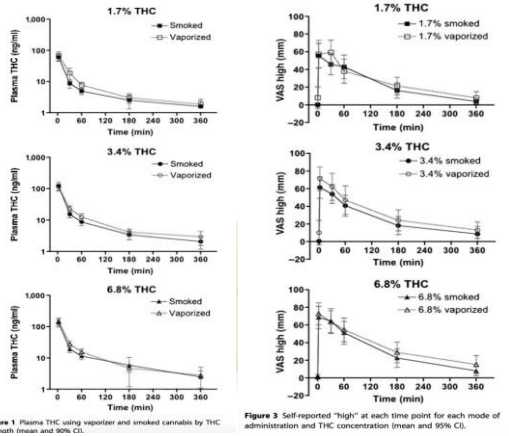


Figure 1 Plasma THC using vaporizer and smoked cannabis by THC strength (mean and 90% CI).

Figure 3 Self-reported "high" at each time point for each mode of administration and THC concentration (mean and 95% CI).

12

High THC Flower Studies

- Passive, vaporized, ingested, smoked
- High THC (13%) Cannabis obtained from NIDA
- PL, 10mg, 25m

* Oral administration only

13

Biological Specimens

- Whole blood: THC, 11-OH-THC, and THCCOOH (LOQ = 0.5ng/mL)
- Urine: THCCOOH (LOQ = 0.75ng/mL)
- Saliva/oral fluid: THC and THCCOOH (LOQ = 2 and 0.02 ng/mL respectively)

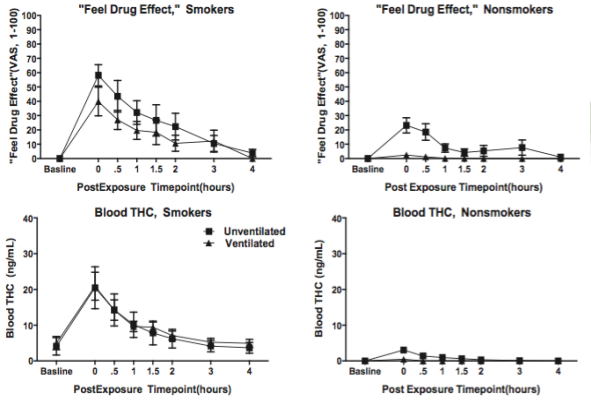
14

Passive Exposure Study

- 3 test sessions; 12 participants per session
  - 5.3% THC cannabis; no ventilation
  - 11% THC cannabis; no ventilation
  - 11% THC cannabis; ventilation
- 6 smokers (ad-lib) and 6 passively exposed
- 60-minute exposure period

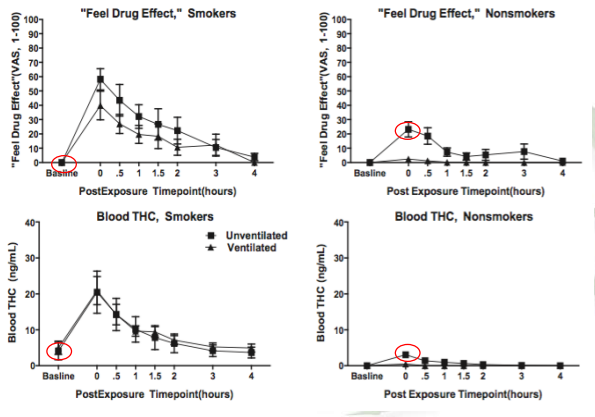
15

Direct Vs. Passive



16

Can I Get a Contact High?



17

Study Summary

- Modest subjective and performance effects for 1-2 hrs
- Urine: Cmax, 2-11 hrs; >15 ng/mL, 2-30 hrs
- OF: Cmax = 0.25 hr; > 4 ng/mL, 0.25-2 hrs
- Blood: Cmax = 0.25-2 hrs; Two > 5 ng/mL

18

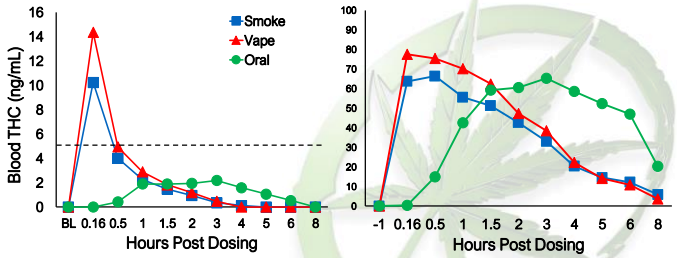
Oral, Smoked, Vaped

- Healthy adults with prior cannabis use; not in past 3 months
- 3 separate studies; 2 oral, 1 smoke + vape
- Balance of males and females
- Standard low-fat breakfast provided

19

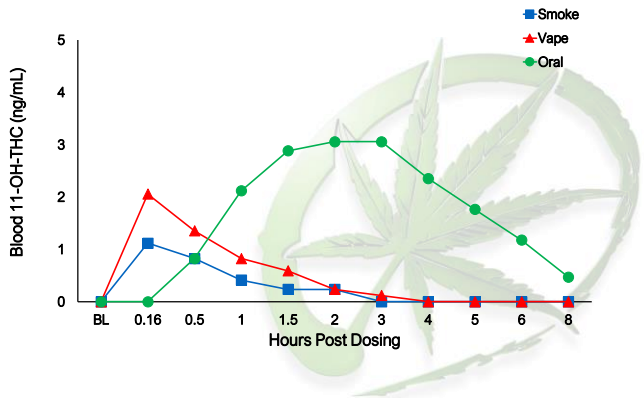
Blood THC + Drug Effect

25mg THC Dose



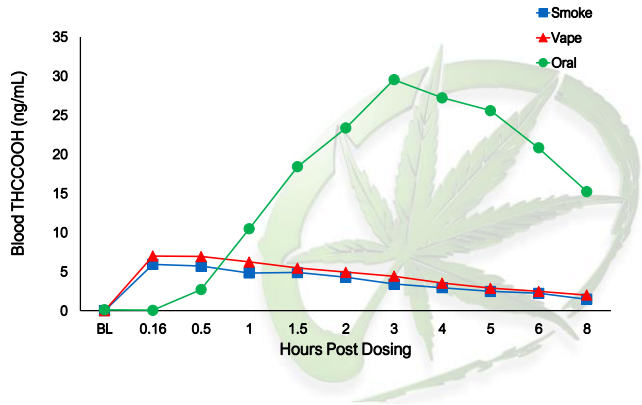
20

Blood 11-OH-THC (25mg)



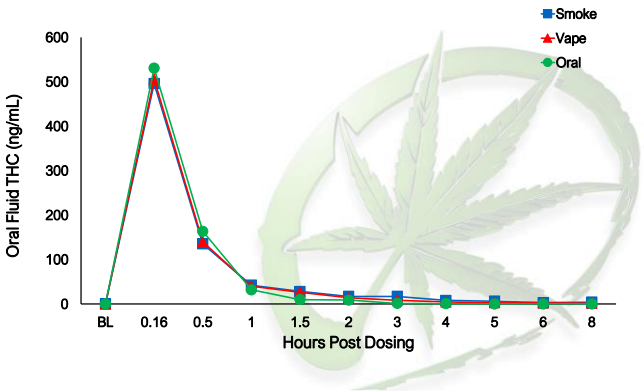
21

Blood THCCOOH (25mg)



22

Oral Fluid THC (25mg)



23

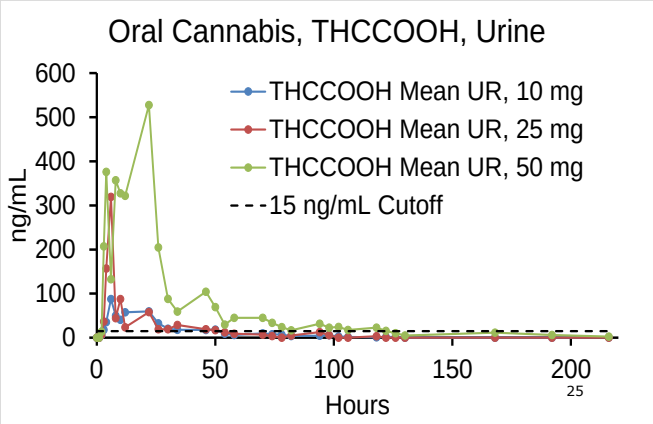
Oral Cannabis Blood/OF

Dose, mg	THC Cmax (ng/mL)	THC Tmax (h)	11-OH-THC Cmax (ng/mL)	11-OH-THC Tmax (h)	THCCOOH Cmax (Blood, ng/mL, Oral Fluid, pg/mL)	THCCOOH Tmax (h)
Blood						
10	1.0 (0 - 3)	0.9 (0 - 2)	1.0 (0 - 2)	1.3 (0 - 3)	7.2 (5 - 14)	3.2 (2 - 4)
25	3.5 (3.0 - 4)	2.6 (1.0 - 4)	3.3 (2 - 5)	3.0 (1.5 - 4)	21.3 (12 - 39)	3.3 (1.5 - 6)
50	3.3 (1.0 - 5)	2.3 (1.0 - 6)	3.2 (2 - 4)	1.8 (1 - 3)	29.3 (16 - 44)	3.3 (1.5 - 8)
Oral Fluid						
10	191.5 (47 - 412)	0.2 (0.2 - 0.5)	NT	NT	50.8 (0 - 231)	1.0 (0 - 3)
25	477.5 (70 - 1128)	0.2 (0.2 - 0.5)	NT	NT	139.7 (23 - 251)	9.8 (3 - 30)
50	597.5 (350 - 1010)	0.2 (0.2 - 0.5)	NT	NT	314.3 (0 - 822)	17.4 (0 - 54)

24

24

Oral Cannabis Urine



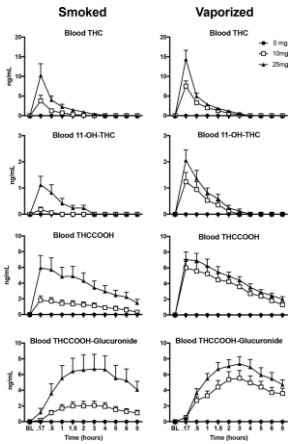
25

Additional Observations

- Window of detection was 0-22, 1.5–22, and 74-216 hours for blood, OF and urine
- 2 at 10mg had no THC in blood
- 2 at 50mg had 5ng/mL; none exceeded
- Inhaled THC in blood: Cmax = 42-87ng/mL; Tmax = <10min; Return to baseline 3-6hrs

26

Smoke/Vape Cannabis Blood



27

27

What Does 2-5ng/mL THC in Blood Mean?

- Daily user, overnight abstinent, no drug effect
- Non-user, 60-min extreme passive exposure, mild drug effect
- Ate a 50mg THC brownie, severely impaired
- Inhaled 25mg THC about 30min ago, significantly impaired, but will be negative by the time blood is drawn

28

CBD Study

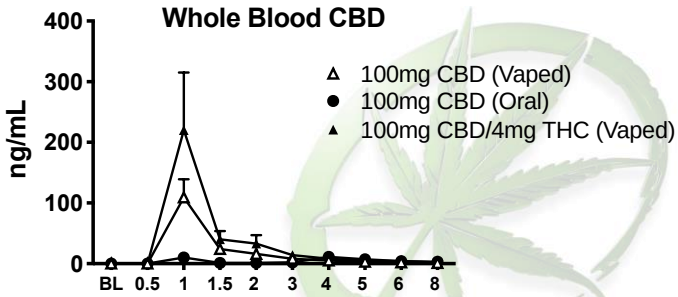
- 4 dose conditions, double-blind, double-dummy

1) Placebo capsule, placebo cannabis
2) 100mg CBD capsule, placebo cannabis
3) Placebo capsule, 100mg CBD Vaporized
4) Placebo capsule, 100mg CBD+4mg THC Vaporized

- Cannabis obtained from NIDA; CBD obtained from AMRI Global
- Oral doses were gelcaps filled with drug/cellulose
- Vaporization completed with The Volcano Medic

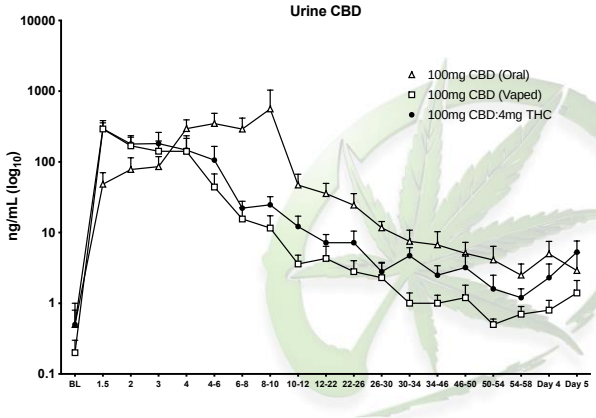
29

Whole Blood CBD



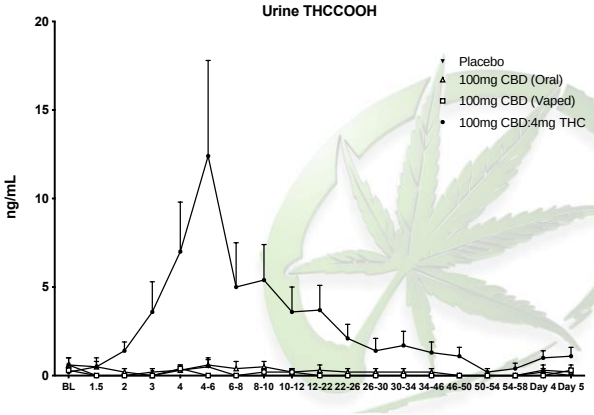
30

Urine CBD



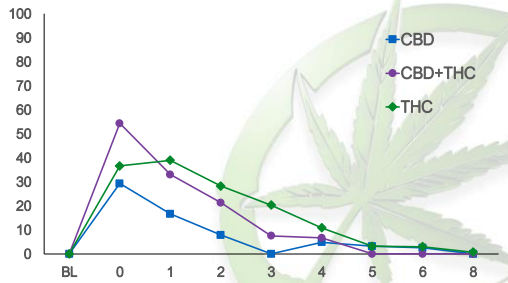
31

Urine THCCOOH



32

Subjective Drug Effects
4/5mg THC Dose/100mg CBD



33

Drug-Drug Interactions

- GW Pharma observed 500% increase in clobazam during CBD (Epidiolex) trial
- Pre-clinical modeling studies indicate potential impact of THC or CBD on metabolism of five CYP450 pathways: CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A
- Human lab study in preparation and expected to be completed this year

34

Summary

- Route of administration impacts the time course of drug effects and biomarkers
- Blood cannabinoids do not always reflect drug effects – effect of lipophilic nature
- Low correlations with OF cannabinoids and PD
- Determining impairment with a single biomarker that can account for route of administration differences is not yet feasible
- Need data on other formulations, routes and constituent chemicals

35

Thanks!!

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36