An analysis of the pharmacokinetic variability of oral cannabidiol and its major metabolites in healthy volunteers

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BACKGROUND

Cannabidiol (CBD) is a widely utilized nonpsychoactive cannabinoid available as an OTC supplement, a component of medical cannabis, and a prescriptive treatment of childhood epilepsies[1]. Epidiolex® CBD solution is the first FDA-approved therapeutic derived from cannabis indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome. Additional pharmacological activity has been attributed to CBD through *in vitro* research and clinical use, including anti-inflammatory and anti-oxidative effects [1].

In humans, 7-OH-CBD has been identified as the major active metabolite possessing similar pharmacological activity to the parent compound. [2] Additionally, 7-COOH-CBD is a major inactive metabolite formed from 7-OH-CBD, which attains concentrations exceeding those of the parent compound after oral administration [3].

In humans, CBD is primarily metabolized by CYP2C19 and CYP2C9, while the enzyme(s) responsible for the conversion of 7-OH-CBD to 7-COOH-CBD remains unidentified [4] (Figure 1).

Recent clinical research has revealed significant variability in the pharmacokinetics (PK) of CBD [5]. However, the underlying factors contributing to this variability, particularly after long-term CBD administration, remain unclear.

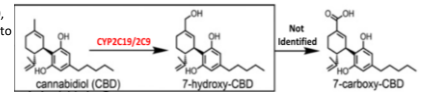
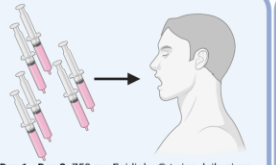


Figure 1. The major metabolic pathway for CBD.

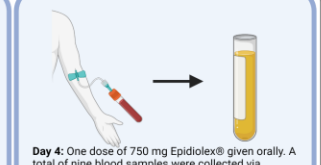
Additionally, there is a dearth of human studies investigating the PK of CBD metabolism in 7-OH-CBD and 7-COOH-CBD during multiple and high oral dosages of CBD administration. To address this void, a preliminary analysis was conducted of the PK of CBD during a multiple-oral-dose administration and its biotransformation. We were able to further analyze blood samples collected from healthy subjects (n=12) who participated in a previously conducted CBD drug interaction study[6].

METHOD

- The study protocol was approved by the University of Florida Investigational Review Board (NCT04603391).
- 12 subjects (6 male, 6 female) completed the entire protocol.
- CBD were well-tolerated. No severe side-effect observed.

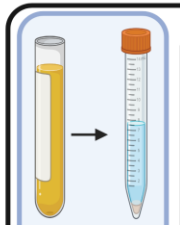


Day 1 - Day 3: 750 mg Epidiolex® twice daily given orally for 3 days.

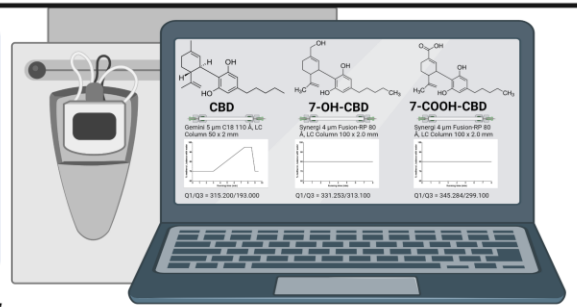


Day 4: One dose of 750 mg Epidiolex® given orally. A total of nine blood samples were collected via indwelling venous catheter. Plasma samples were collected to be analyzed.

Study Design and Drug Administration



Liquid-liquid extraction with a solution of 4:1 butyl chloride/acetonitrile



Analytical Method

- Statistical Analysis were performed by SAS 9.
- Non-compartmental analysis was applied to calculate peak plasma concentration (Cmax) and area under the curve (AUC) for CBD, 7-OH-CBD and 7-COOH-CBD.
- Patients' demographic data were used for correlation analysis with the following covariant: Race, Age, Sex, Height, Weight, and BMI.

Statistical Analysis

SELECT RESULTS

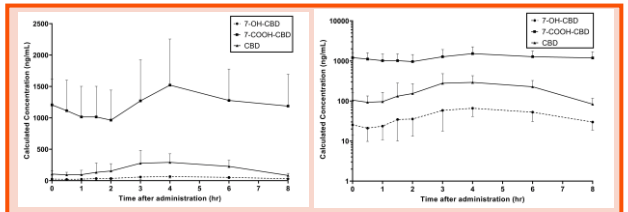


Figure 2. Plasma concentration vs time plot of CBD, 7-OH-CBD, and 7-COOH-CBD after the last dose of CBD. 12 subjects. Mean with SD.
Left: linear scale.
Right: logarithmic scale.

Race	Age (years)	Sex	Weight (Kg)	Height (cm)	BMI
Mestiza	31	Female	53	160	20.7
Black	30	Male	60.3	161	23.3
White	27	Male	79.2	170	27.4
Asian	44	Female	51.6	157	20.9
White	23	Male	78.5	185.3	22.9
White	25	Female	59	174.5	19.4
White	22	Male	90	180.9	27.5
Asian	21	Female	66.9	155.6	27.6
Hispanic	21	Male	54.2	171.3	18.5
Native American	29	Female	53.1	154.1	22.4
Asian	26	Male	87.1	183	26
White	21	Female	56.9	169.2	19.9

Table 1. Demographic data for test subjects.

7-COOH-CBD						
Variable	Mean	Std Dev	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
Tmax (hr)	4.33	1.50	3.38	5.28	1.00	6.00
Cmax (ng/mL)	1717.33	769.22	1228.59	2206.07	813.00	3100.00
AUC (ng/mL*hr)	9888.42	3961.47	7371.42	12405.42	4890.00	18143.00
7-OH-CBD						
Variable	Mean	Std Dev	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
Tmax (hr)	4.25	1.42	3.35	5.15	2.00	6.00
Cmax (ng/mL)	81.35	36.64	58.07	104.63	30.00	173.00
AUC (ng/mL*hr)	364.70	105.59	297.61	431.79	188.10	554.20
CBD						
Variable	Mean	Std Dev	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
Tmax (hr)	4.08	1.62	3.05	5.11	1.00	6.00
Cmax (ng/mL)	389.17	153.23	291.81	486.52	177.00	648.00
AUC (ng/mL*hr)	1542.19	488.04	1232.10	1852.28	737.30	2331.00

Table 2. PK analysis for CBD, 7-OH-CBD, and 7-COOH-CBD.

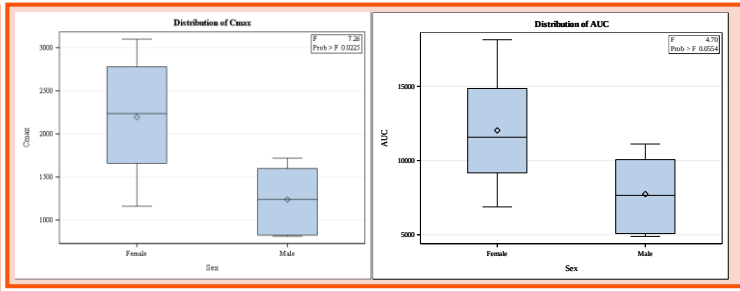


Figure 3. T-test for C_{max} and AUC with sex.
Left: The C_{max} for females was significantly higher than that in males receiving the same dosage (P = 0.0225).

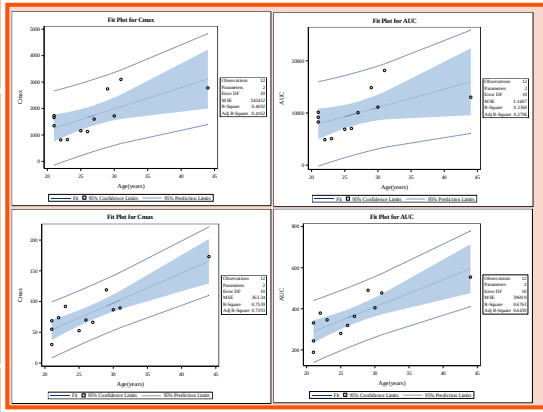


Figure 4. Regression analysis of C_{max} and AUC to age.

Statistically significant linearity found for C_{max} to age on 7-COOH-CBD (P = 0.0140) upper left, 7-OH-CBD (P = 0.0002) lower left.

Statistically significant linearity found for AUC to age on 7-COOH-CBD (P = 0.0479) upper right, 7-OH-CBD (P = 0.0010) lower right.

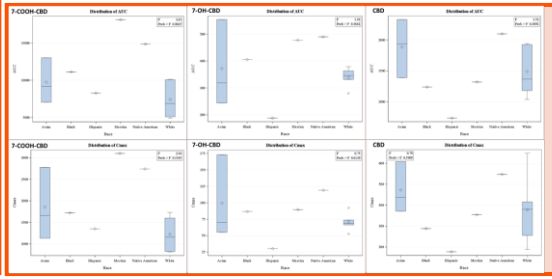


Figure 5. One-way ANOVA of AUC and C_{max} for CBD and its major metabolites.
Findings were not significant, P values for individual ANOVA were shown with the graph)

Upper row: AUC, Lower row: C_{max}.
Left column: 7-COOH-CBD, Middle column: 7-OH-CBD, Right column: CBD.

CONCLUSION

- **A statistically significant difference in 7-COOH-CBD C_{max} was found between males and females (P = 0.0225).**
- **There was a linear relationship between C_{max} and age as well as AUC and age for both metabolites (7-OH-CBD and 7-COOH-CBD).**
- **PK differences based on race/ethnicity could not be evaluated due to the limited number of subjects**
- **Further modeling analysis is required to distinguish drug distribution and metabolic parameters.**
- **Additional population-based PK analysis is planned to help identify the contribution of variability.**

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ACKNOWLEDGEMENTS

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