An Assessment of the Influence of Cannabidiol on the Pharmacokinetics of Methylphenidate

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Consortium for Medical Marijuana Clinical Outcomes Research

BACKGROUND

Medical cannabis [*Cannabis sativa L.* (marijuana)] or one or more of its components can be used medicinally in 36 US states. Cannabis is comprised of over 500 different chemical components approximately 120 of which are cannabinoids. The most abundant and well-studied cannabinoids are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Previous *in vitro* studies suggest that THC and CBD can potently inhibit major CYP450 isoforms CYP2D6, CYP2C19, CYP2C9, CYP2B6, and CYP1A2.[1] Thus, the concomitant use of cannabis with conventional medications poses a potential risk of drug-drug interactions (DDIs). More recently *in vitro* studies have indicated that CBD and other major cannabinoids were potent inhibitors to the human carboxylesterase 1 (CES1) [2].

The present study was conducted to determine if in vitro findings with CES1 could be confirmed in a clinical study. Specifically, this study addressed the question of whether CBD could inhibit CES1 to a clinically relevant extent in healthy subjects (n=12). A randomized placebo controlled, cross-over study design was employed in which purified CBD (administered as Epidiolex®) was given concomitantly with the recognized CES1 substrate, the psychostimulant methylphenidate (MPH, Ritalin®).

MPH is almost exclusively metabolized by CES1 and therefore served as a representative "probe" of alterations in CES1 activity. Findings in this study may have implications for numerous other therapeutic agents which are also dependent on CES1 for either inactivation or activation (ie prodrugs).

Table 1: CES1 drug class and medication substrates.

ACE inhibitors	**Anticancer Agents**	**Antihyperlipidemics**
Benazepril Perindopril	Capecitabine	Simvastatin
Enalapril Quinapril	Irinotecan	Lovastatin
Imidapril Ramipril	Telotristat etiprate	Clofibrate
Moexipril Trandolapril	**CNS Agents**	Fenofibrate
Antiplatelets/Anticoagulants	Methylphenidate	**Immunosuppressive**
Clopidogrel	Heroin	Mycophenolate mofetil
Dabigatran etexilate	Meperidine	Ciclesonide
Endogenous compounds	Flumazenil	**Antiviral Agents**
Cholesterol	Rufinamide	Oseltamivir
Fatty acid ethyl esters	Cocaine	Sofosbuvir
		Tenofovir alafenamide

OBJECTIVES

- To determine if the single-dose pharmacokinetics of methylphenidate (Ritalin®) are altered by concomitant use of Epidiolex® (CBD).
- To determine if the single-dose pharmacokinetics of MPH is altered to the inactive components in the vehicle solution.

METHODS

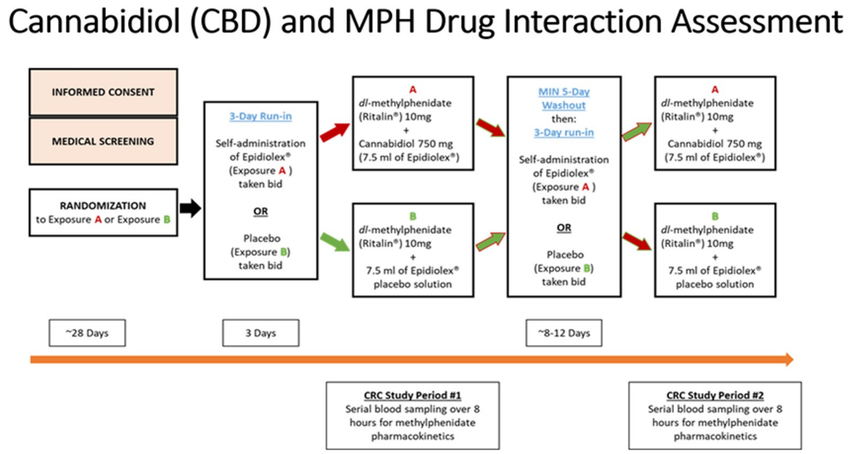

Figure 1. Design of the clinical study.

An IRB-approved study was conducted at the UF CTSI, This was an open-label and placebo-controlled randomized crossover design with a 30-day run-in of CBD 750 mg twice daily exposure conducted in healthy subjects (n-12).

Laboratory Assay

- Liquid-liquid extraction for MPH and CBD.
- LC-MS/MS for quantification.

Pharmacokinetics Analysis

- Bioequivalence analysis was following FDA Guidance.
- Bioequivalence criteria (0.8 – 1.25) were used to determine the difference of the AUC_{total}, and C_{max}
- Non-compartmental PK analysis.
- Non-linear regression.
- Analyzed with SAS 9®.

CONCLUSIONS

- Co-administration of CBD **is not bioequivalent** with control.
- **8 of 12** subjects experienced an **AUC_{total} increase** with the maximum being 1.49-fold higher in the CBD group when compared to placebo.
- **C_{max} was increased** in **8** of the subjects' CBD arms (maximum 2-fold increase) and **$t_{1/2}$ was increased** in **6** of the subjects CBD arms (maximum 1.48-fold increase).
- In some subjects there existed a potential DDI liability with the coadministration of CBD and MPH.

FUTURE DIRECTIONS

- Collected plasma samples are presently under analysis to determine CBD exposure and pharmacokinetics and to explore potential correlations between CBD concentrations and CES1 inhibition

KEY REFERENCES

1. Qian Y Gurley BJ, Markowitz JS. The potential for pharmacokinetic interactions between cannabis and conventional medications. *J Clin Psychopharmacol* 2019;39(5):462-471.
2. Qian Y, Wang X, Markowitz JS. In vitro inhibition of carboxylesterase 1 by major cannabinoids and selected metabolites. *Drug Metab Dispos*. 2019;47(5):465-472.

ACKNOWLEDGMENTS

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❖ Epidiolex® and Epidiolex® Placebo were generously donated by Greenwich Biosciences Inc

RESULTS

Subjects

- Twelve (12) subjects (6 male, 6 female) ages 21-44 (mean 27 years) completed the entire study protocol.
- Both MPH and CBD were generally well-tolerated without any serious adverse effects.
- One subject experienced nausea and vomiting from CBD and discontinued the study and was replaced by an alternate.
- No subject experienced elevations in any monitored liver function test.

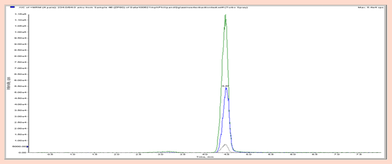

Figure 2. Chromatogram for MPH (blue) and internal standard d4-MPH (green).

Table 2. Pharmacokinetic analysis of each individual subject for both the CBD and control groups which includes AUC_{total}, C_{max}, AUC_{total} ratio (CBD/control), and C_{max} ratio (CBD/control)

Subject ID	Treatment AUC_{total} (ng/mL*hr)	Control AUC_{total} (ng/mL*hr)	AUC_{total} Ratio (CBD/Control)	Treatment C_{max} (ng/mL)	Control C_{max} (ng/mL)	C_{max} Ratio (CBD/Control)
ID01	90.02	62.80	1.43	23.20	14.40	1.61
ID02	83.38	71.23	1.17	14.70	13.30	1.11
ID03	99.90	98.57	1.01	13.60	16.70	0.81
ID04	103.32	68.98	1.50	14.70	10.80	1.36
ID07	94.01	78.76	1.19	26.50	13.20	2.01
ID08	48.34	44.67	1.08	10.00	6.60	1.52
ID09	38.57	42.57	0.91	8.39	8.96	0.94
ID10	63.94	50.37	1.27	10.80	9.06	1.19
ID11	56.07	67.95	0.83	8.97	22.80	0.39
ID12	61.74	60.08	1.03	13.50	12.90	1.05
ID13	69.36	70.08	0.99	10.70	8.47	1.26
ID14	39.86	46.63	0.85	6.92	9.15	0.76

Pharmacokinetics

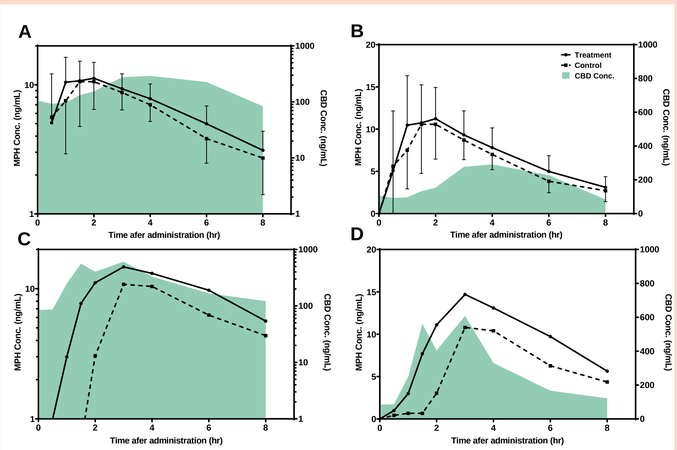

Figure 3. Plasma concentration vs time curves of a single subject as well as mean of all subjects (n=12).

Left y-axis: MPH plasma concentration (ng/mL), right y-axis: CBD plasma concentration (ng/mL), x-axis: time after administration (hr).

Panel A: MPH and CBD plasma concentration of an individual subject (ID04) plotted on a logarithmic scale.

Panel B: MPH and CBD plasma concentration of the same individual subject plotted on a linear scale.

Panel C: MPH and CBD plasma concentration of the mean data points of all subjects plotted on a logarithmic scale.

Panel D: MPH and CBD plasma concentration of the mean of all subjects plotted on a linear scale.

Table 3. Bioequivalence analysis to CBD vs. control arm. CV: coefficient of variant, CI: confidential interval.

Parameters	Treatment				Control				GMR (Treatment/Control)	
	Mean	%CV	Range		Mean	%CV	Range		CI (90%)	
C_{max}/kg (ng/mL*hr)	12.80	57.86	4.41	31.31	14.01	54.22	5.67	26.93		
AUC_{last} (ng/mL*hr)	53.76	29.83	31.60	80.70	49.55	25.25	30.70	74.32		
ke (/hr)	0.21	22.03	0.15	0.31	0.24	30.61	0.15	0.39		
T_{max} (hr)	[1.25]*	/	0.50	3.00	[1.75]*	/	0.50	3.00		
AUC_{total} (ng/mL*hr)	66.65	32.53	38.57	103.32	63.56	25.45	42.57	98.57	1.09	0.89 1.32
C_{max} (ng/mL)	12.15	43.73	6.92	26.50	12.20	36.42	6.60	22.80	1.08	0.85 1.37

*T_{max} was expressed as median and range.

Table 4. Pharmacokinetic analysis of CBD.

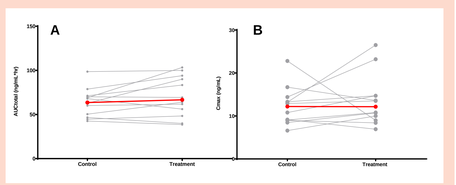

Figure 4. MPH pharmacokinetics charges individual subjects between control and treatment groups. **Pannal A:** total AUC change. **Pannal B:** C_{max} change. Red points and lines represent the average.

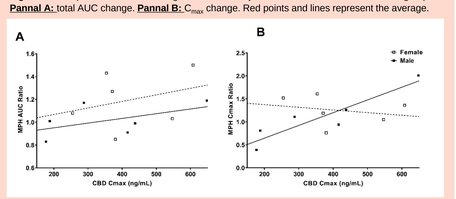

Figure 5. Correlation of CBD C_{max} and MPH AUC and C_{max} ratio in male and female subjects. **Panel A:** linear regression of CBD C_{max} and MPH AUC, for male: r^2 =0.2712 , for female: r^2 = 0.09153. **Panel B:** linear regression of CBD C_{max} and MPH AUC, for male: r^2 = 0.8403, for female: r^2 = 0.05879.