Prediction of Pharmacokinetic Interactions between Methylphenidate and Cannabinoids

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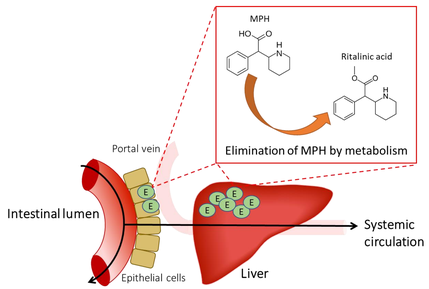
INTRODUCTION

Methylphenidate (MPH) is a first-line medication for treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. ADHD is a neuropsychiatric disorder characterized by inattention, impulsive/hyperactive behaviors, and/or poor academic performance. The symptoms of ADHD persist into adulthood for most of the children,[1] and there are approximately 4.4% adults in the US and 2.8% adults worldwide reported to be affected by ADHD.[2]



After oral administration, the absorption of MPH is almost complete, and extensive enantioselective pre-systemic metabolism has been documented with the pharmacologically active d-MPH isomer achieving much higher systemic levels. MPH is mainly eliminated through biotransformation by the hepatic esterase carboxylesterase 1 (CES1) to its inactive metabolite ritalinic acid, which accounts for up to 80% of all MPH species recovered in the urine.[3,4]

Cannabis (Cannabis sativa L.; marijuana) products are commonly used both recreationally and medically in the US, and it is perceived by some ADHD patients as potential medications for improving ADHD symptoms or other comorbid conditions.[5] In addition, **Epidiolex®**, an FDA-approved oral solution of cannabidiol (CBD), is indicated for treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.

Finally, recent in vitro investigations indicates that several of the major cannabinoids are potent inhibitors of CES1.[6] Therefore, co-exposure to MPH and cannabinoids is likely which requires investigation of potential **drug-drug interactions (DDI)**.

OBJECTIVES

1. To determine the kinetic parameters of DDI between cannabinoids and MPH in an in vitro system and predict the clinical outcomes by both static and physiologically-based pharmacokinetic (PBPK) models.
2. To design a clinical study to verify the DDI predicted between Ritalin® (dl-MPH) and Epidiolex® (CBD).

METHODS

- An *in vitro* system comprised of human liver S9 (HLS9) was employed to represent the metabolism of MPH in the liver. The formation velocities of the metabolite ritalinic acid were measured by LC-MS/MS (Figure 1). Unbound fractions of THC and CBD in the in vitro incubation mixture (Figure 2) were determined and utilized in further inhibition studies.
- Inhibition by the major cannabinoids Δ^9-tetrahydrocannabinol (THC) and CBD was assessed by addition of them into the in vitro incubation mixture (Figure 3 and 4). The inhibition constants (K_i) were estimated by fitting a mixed competitive-noncompetitive inhibition model into the data (Table 1):

$$v = \frac{V_{max} \cdot [S]}{K_m\left(1+\frac{[I]}{K_i}\right)+[S]\left(1+\frac{[I]}{\alpha \cdot K_i}\right)}$$

where V_{max} and K_m represent the maximum reaction rate and the Michaelis-Menten constant, respectively. The variables are v, the observed metabolite formation rate; [S], the substrate concentration; and [I], the cannabinoid concentration.

- The potential for clinical interactions between MPH and THC/CBD was first evaluated by a static mechanistic model (Table 2):

$$AUCR = \frac{1}{\frac{1}{1+\frac{[I]_h}{K_i}} \cdot f_m + (1 - f_m)}$$

where AUCR predicts the change in MPH exposure when THC/CBD is co-administered. $[I]_h$ and f_m are the unbound maximum concentration of THC/CBD in the liver and fraction of MPH metabolized by CES1, respectively.

- Further, PBPK models for MPH and CBD were developed and validated to obtain a more precise prediction of clinical interactions between Ritalin® and Epidiolex®. Various clinical scenarios were simulated using the joint PBPK model to assist the design of clinical study (Figure 5 and 6).
- A healthy volunteer study (n=12) assessing the DDI potential for CBD to inhibit MPH metabolism in underway (Figure 7).

RESULTS

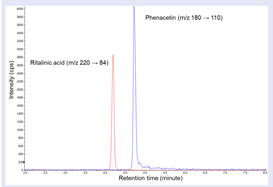


Figure 1. Chromatogram of ritalinic acid and internal standard phenacetin.

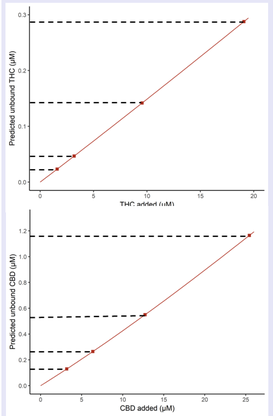


Figure 2. Unbound fractions of THC/CBD in incubation mixtures.

Unbound fractions of THC and CBD were approximately 1.5% and 4.3%, respectively.

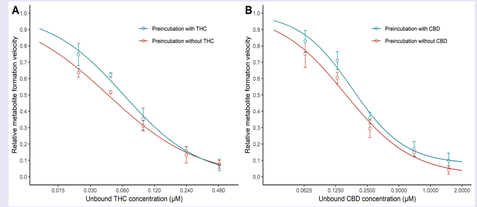


Figure 3. Time-dependent inhibition study.

Green represents samples pre-incubated with THC/CBD. Red represents control samples pre-incubated without THC/CBD. Data points represent the mean (±SD) of triplicate samples. Lines represent model prediction.

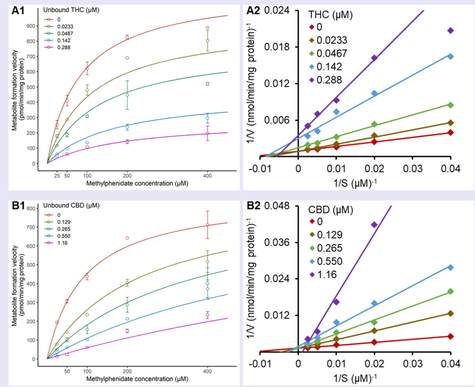


Figure 4. Kinetic analysis and Lineweaver-Burk plots of inhibition of MPH hydrolysis by THC (panel A1 and A2) and CBD (panel B1 and B2).

HLS9 was incubated with varying concentrations of MPH and THC or CBD. Data were from one of three independent experiments. Data points represent mean (±SD) of duplicate sample.

Table 1. Parameter estimates from inhibition kinetic study.

Cannabinoids	K_m (μM)	K_i (μM)	α	V_{max} (pmol/min/mg protein)
THC	85.7 ± 12.9	0.031 ± 0.003	16.4 ± 14.7	1056 ± 77
CBD	90.6 ± 10.1	0.091 ± 0.004	>9999	940 ± 150

Table 2. Prediction of clinical DDI by the static mechanistic model.

Inhibitor	Administration route	Dose	$I_{max,u}$ (μM)	$I_{inlet,max,u}$ (μM)	AUCR
THC	Inhalation	33.8 mg	0.0144	-	1.34
CBD	Oral solution	750 mg twice daily	0.140	0.633	3.33

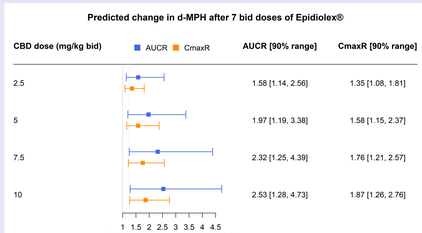


Figure 5. PBPK model simulated changes in d-MPH after co-administration of multiple Epidiolex® doses.

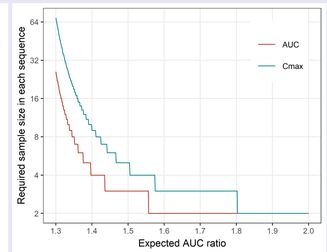


Figure 6. Required sample sizes for the clinical study to achieve at least 80% power.

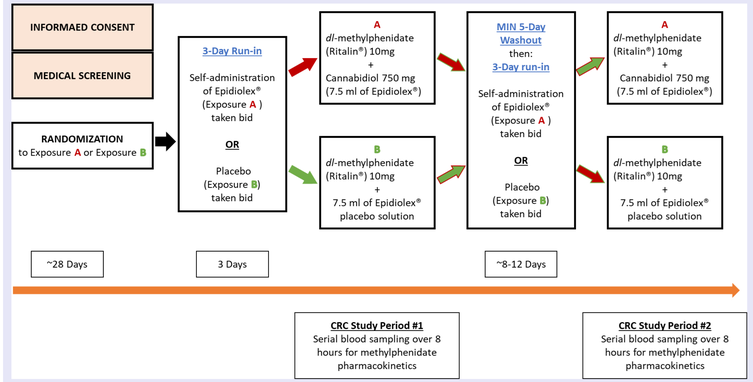


Figure 7. Design of the clinical study.

The study is designed as an open-label and placebo-controlled randomized crossover design. 18 healthy subjects are expected to be screened with the goal of 12 completing the entire protocol.

CONCLUSIONS

- Both THC and CBD exhibited **potent in vitro inhibition** on MPH metabolism by HLS9.
- The static and dynamic (PBPK) mechanistic models predicted **mild inhibition** of MPH metabolism by THC and **moderate inhibition** by CBD in clinical scenarios.
- Our ongoing clinical study (n=12) has enough power to detect the predicted DDI between Ritalin® and Epidiolex ®.

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