Poster: PT-027

Title: Inhibition of Tacrolimus Metabolism by Cannabidiol

Presenter: Gerald So1

1Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

**Supplement**

**Table of Contents**

Table S1 – PK parameters of tacrolimus depletion with pooled HLMs

Table S2 – PK parameters of tacrolimus depletion with rCYP3A4/5

Table S3 – Parameters for PK calculation and extrapolation

Table S4 – Raw data of tacrolimus depletion with pooled HLMs

Table S5 – Raw data of tacrolimus depletion with rCYP3A4

Table S6 – Raw data of tacrolimus depletion with rCYP3A5

**Table S1**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Tacrolimus | Tacrolimus +  Ketoconazole | Tacrolimus +  CBD | Tacrolimus +  7-OH CBD | Tacrolimus +  7-COOH CBD |
| HLM (fumic,HLM = 0.672) |  |  |  |  |  |
| kdep (min-1) | 0.273 (0.249-0.297) | 0.024 (0.019-0.030) | 0.152 (0.138-0.167) | 0.083 (0.074-0.091) | 0.221 (0.195-0.248) |
| t1/2 (min) | 2.54 | 28.4 | 4.56 | 8.39 | 3.13 |
| Fold change of t1/2 | NA | 11.2 | 1.79 | 3.30 | 1.23 |
| CLint,HLM (mL/min/mg microsomal protein) | 0.812 | 0.073 | 0.452 | 0.246 | 0.65 |
| CLint (mL/min/kg) | 835 | 74.7 | 465 | 253 | 678 |
| CLH,B (mL/min) | 0.282 | 0.026 | 0.163 | 0.086 | 0.230 |
| EH,B | 0.014 | 0.001 | 0.008 | 0.004 | 0.012 |

**Pharmacokinetic parameters of tacrolimus depletion with pooled HLMs.** CBD, cannabidiol; CLH,B, hepatic intrinsic clearance of tacrolimus based on blood concentrations; CLint, *in vivo* intrinsic clearance of tacrolimus in a liver; CLint,HLM, *in vitro* intrinsic clearance of tacrolimus in human liver microsomes; EH,B, hepatic extraction ratio of tacrolimus based on blood concentrations; kdep; t1/2, half-life; 7-COOH CBD, 7-carboxycannabidiol; 7-OH CBD, 7-hydroxycannabidiol.

**Table S2**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Tacrolimus | Tacrolimus +  Ketoconazole | Tacrolimus +  CBD | Tacrolimus +  7-OH CBD | Tacrolimus +  7-COOH CBD |
| rCYP3A4 (fumic,rCYP3A4 = 0.885) | | | | | |
| kdep (min-1) | 0.752 (0.650-0.854) | 0.086 (0.049-0.123) | 0.114 (0.076-0.151) | 0.050 (0.015-0.084) | 0.659 (0.563-0.755) |
| t1/2 (min) | 0.922 | 8.06 | 6.11 | 14.0 | 1.05 |
| Fold change of t1/2 | NA | 8.74 | 6.63 | 15.2 | 1.14 |
| CLint,rCYP3A4 (μL/min/pmol rCYP3A4) | 6.37 | 0.729 | 0.962 | 0.420 | 5.59 |
| rCYP3A5 (fumic,rCYP3A5 = 0.885) | | | | | |
| kdep (min-1) | 1.97 (1.32-2.62) | 0.720 (0.615-0.826) | 0.065 (0.047-0.084) | 0.095 (0.056-0.134) | 1.75 (1.36-2.13) |
| t1/2 (min) | 0.351 | 0.962 | 10.6 | 7.30 | 0.397 |
| Fold change of t1/2 | NA | 2.74 | 30.3 | 20.8 | 1.13 |
| CLint,rCYP3A5 (μL/min/pmol rCYP3A5) | 16.7 | 6.11 | 0.552 | 0.804 | 14.8 |

**Pharmacokinetic parameters of tacrolimus depletion with rCYP3A4 and rCYP3A5.** CBD, cannabidiol; CLint,rCYP3A4, *in vitro* intrinsic clearance of tacrolimus in recombinant CYP3A4 enzymes; CLint,rCYP3A5, *in vitro* intrinsic clearance of tacrolimus in recombinant CYP3A5 enzymes; kdep, depletion rate constant; t1/2, half-life; 7-COOH CBD, 7-carboxycannabidiol; 7-OH CBD, 7-hydroxycannabidiol.

**Table S3**

|  |  |  |
| --- | --- | --- |
| Parameters | Value | Source |
| Tacrolimus | | |
| logP | 3.26 | (Gertz et al, 2011)1 |
| fuP | 0.012 ± 0.0012 | (Zahir et al, 2001)2 |
| B/P ratio | 35 | (Zahir et al, 2001)2 |
| Physiological | | |
| MPPGL | 40 mg | (Hakooz et al, 2006)3 |
| LW/BW (Based on a 70-kg human) | 25.7 g/kg | (Davies and Morries, 1993)4 |
| QH,B (Based on a 70-kg human) | 19.6 mL/min/kg | (Davies and Morries, 1993)4 |

**Parameters for pharmacokinetic calculation and extrapolation.** B/P ratio, blood-to-plasma ratio; fuP, fraction unbound in plasma; logP, partition coefficient between octanol and water; LW/BW, liver weight per body weight; MPPGL, microsomal protein per gram of liver; QH,B, hepatic blood flow per body weight.

**Table S4**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Time (min) | Tacrolimus | Tacrolimus + Ketoconazole | Tacrolimus + CBD | Tacrolimus + 7-OH CBD | Tacrolimus + 7-COOH CBD |
| 0 | 100 | 100 | 100 | 100 | 100 |
| 5 | 48.8 ± 3.22 | 95.2 ± 15.0 | 65.0 ± 11.4 | 64.6 ± 6.46 | 55.3 ± 7.98 |
| 10 | 15.4 ± 3.30 | 88.5 ± 8.47 | 30.6 ± 4.73 | 42.3 ± 5.85 | 19.3 ± 5.72 |
| 15 | 2.18 ± 0.379 | 75.3 ± 7.97 | 12.5 ± 2.54 | 24.9 ± 8.49 | 5.64 ± 4.07 |
| 20 | 0.537 ± 0.173 | 61.0 ± 9.72 | 5.26 ± 1.39 | 16.5 ± 4.13 | 1.40 ± 0.410 |
| 30 | 0.481 ± 0.229 | 51.3 ± 8.49 | 3.44 ± 0.552 | 9.06 ± 1.54 | 0.513 ± 0.165 |

Descriptive statistics of percent tacrolimus remaining with pooled HLMs. Data are presented in mean ± SD (%).

**Table S5**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Time (min) | Tacrolimus | Tacrolimus + Ketoconazole | Tacrolimus + CBD | Tacrolimus + 7-OH CBD | Tacrolimus + 7-COOH CBD |
| 0 | 100 | 100 | 100 | 100 | 100 |
| 1 | 81.8 ± 64.3 | 107 ± 27.8 | 82.9 ± 23.4 | 75.4 ± 0.998 | 42.9 ± 9.44 |
| 2.5 | 27.1 ± 20.0 | 104 ± 9.87 | 53.9 ± 9.84 | 79.7 ± 9.39 | 12.0 ± 5.38 |
| 5 | 4.91 ± 4.71 | 77.4 ± 25.8 | 47.4 ± 9.16 | 67.9 ± 12.2 | 2.26 ± 0.004 |
| 7.5 | 0.413 ± 0.062 | 68.2 ± 20.7 | 30.4 ± 0.627 | 59.8 ± 12.0 | 0.768 ± 0.350 |
| 10 | 0.068 ± 0.009 | 42.7 ± 2.82 | 33.6 ± 1.24 | 59.9 ± 26.2 | 1.07 ± 0.253 |

Descriptive statistics of percent tacrolimus remaining with rCYP3A4. Data are presented in mean ± SD (%).

**Table S6**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Time (min) | Tacrolimus | Tacrolimus + Ketoconazole | Tacrolimus + CBD | Tacrolimus + 7-OH CBD | Tacrolimus + 7-COOH CBD |
| 0 | 100 | 100 | 100 | 100 | 100 |
| 1 | 5.47 ± 2.01 | 32.6 ± 3.17 | 75.0 ± 7.77 | 67.5 ± 13.7 | 10.4 ± 1.36 |
| 2.5 | 0.661 ± 0.236 | 7.80 ± 0.728 | 69.5 ± 6.00 | 53.3 ± 2.54 | 1.23 ± 0.471 |
| 5 | 0.254 ± 0.014 | 1.36 ± 0.518 | 60.9 ± 0.701 | 45.2 ± 10.1 | 0.530 ± 0.019 |
| 7.5 | 0.238 ± 0.064 | 0.441 ± 0.034 | 51.2 ± 2.32 | 36.1 ± 7.93 | 0.390 ± 0.222 |
| 10 | 0.370 ± 0.333 | 0.327 ± 0.059 | 48.4 ± 4.54 | 36.0 ± 9.84 | 0.908 ± 0.597 |

Descriptive statistics of percent tacrolimus remaining with rCYP3A5. Data are presented in mean ± SD (%).

**References**

1. Gertz M, Houston JB, Galetin A. Physiologically based pharmacokinetic modeling of intestinal first-pass metabolism of CYP3A substrates with high intestinal extraction. *Drug Metab Dispos*. Sep 2011;39(9):1633-42. doi:10.1124/dmd.111.039248

2. Zahir H, Nand RA, Brown KF, Tattam BN, McLachlan AJ. Validation of methods to study the distribution and protein binding of tacrolimus in human blood. *J Pharmacol Toxicol Methods*. Jul-Aug 2001;46(1):27-35. doi:10.1016/s1056-8719(02)00158-2

3. Hakooz N, Ito K, Rawden H, et al. Determination of a human hepatic microsomal scaling factor for predicting in vivo drug clearance. *Pharm Res*. Mar 2006;23(3):533-9. doi:10.1007/s11095-006-9531-2

4. Davies B, Morris T. Physiological parameters in laboratory animals and humans. *Pharm Res*. Jul 1993;10(7):1093-5. doi:10.1023/a:1018943613122