Model-based analysis on systemic availability of coadministered cannabinoids after controlled vaporised administration

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Key words: medicinal cannabis, cannabinoid, Δ⁹-tetrahydrocannabinol (THC), cannabidiol (CBD), pharmacokinetics, population pharmacokinetics model

ABSTRACT

Aims The most important two medicinal cannabinoids are Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD). Vaporised administration is superior due to its higher systemic availability, lower individual variability and faster drug delivery. Although it is common THC is coadministered with CBD, the influence of CBD on the pharmacokinetics, especially the systemic availability of THC after vaporised administration, is unknown. This study aimed to investigate the influence of different doses of coadministered CBD on the systemic availability of THC, and to compare the availability of THC and CBD in a sample of frequent and infrequent cannabis users.
Methods The study used a randomised, double-blind, crossover placebo-controlled design. THC and/or CBD in ethanol was vaporised and inhaled. Plasma concentrations of THC and CBD were analysed. The THC data created in this study were pooled together with published THC pharmacokinetic data in order to cover all the phases of THC disposition. Population pharmacokinetic model of THC was developed based on the pooled data. The model of CBD was developed based on the data created in this study.

Results Population pharmacokinetic models of THC and CBD were developed. With concomitant inhalation of high dose CBD, the systemic availability of THC decreased significantly. Frequent cannabis users appeared to have higher systemic availability of THC and CBD when high dose CBD was administered.

Conclusions The results observed in this study are useful for guiding future pharmacokinetic studies of medicinal cannabinoids, and for development of dosing guidelines for medical use of cannabis in the ‘real world’ setting.

INTRODUCTION

Medicinal cannabis has been receiving significantly more attention by the community due to its purported therapeutic benefits [1]. As the most well-known cannabinoid in cannabis, Δ⁹-tetrahydrocannabinol (THC) can be used therapeutically, e.g. for wasting syndrome, nausea and vomiting in cancer patients receiving chemotherapy, chronic neuropathic pain management, spasticity in multiple sclerosis, and other indications [2,3]. Another important phytocannabinoid is cannabidiol (CBD), which is the second most abundant cannabinoid in cannabis plant matter and is a non-intoxicating agent with an interesting array of potential therapeutic indications, due to its antiepileptic, anxiolytic, antipsychotic, antiemetic, and anti-inflammatory properties [4,5,6].

Knowledge of the pharmacokinetics (PK) of THC and CBD when delivered by different routes of administration is essential for selection of the best route of delivery and dosing regimen in the clinical setting. As evident from the chemical structures of THC and CBD [7], they are very lipophilic and exhibit poor oral bioavailability with significant inter- and intra-individual variability [8,9]. This low and variable bioavailability may result from pharmacogenetic variability in first pass metabolism, inhibition and saturation of key metabolic pathways, inter-individual variability in gastrointestinal absorption and the effect of food or formulation. The smoked route is still the most commonly used route of administration for recreational users. However, the existence of toxicity due to pyrolytic compounds in smoke disadvantages this route for sick patients. Vaporised route of administration of cannabis plant matter, or of specific cannabinoid compounds, is of interest both therapeutically and in ongoing research into drug effects. This is because the vaporised route has higher systemic availability and lower inter- and intra-individual variability, and
immediate drug delivery compared to the oral route, and less toxicity than the smoked route [10].

Model-based analysis is an efficient method for understanding the pharmacokinetics, the systemic availability and drug exposure of vapourised THC and CBD to ensure optimal efficacy and minimise unwanted effects in the therapeutic space. Strougo et al. [11] developed a PK model of inhaled THC using a vaporiser. Heuberger et al. [12] developed a population PK model (i.e. the study of variability in drug concentrations, pharmacological parameters, e.g. clearance within a patient population using mathematical models) after an oral, intravenous and pulmonary dose of THC in frequent and infrequent cannabis users. Notably, the works of Strougo and Heuberger focused on the PK study of vapourised pure THC. However, it is common that THC is coadministered with CBD, because CBD is frequently concomitant with THC in cannabis plant matter and also might be intentionally dosed together with THC due to its therapeutic benefits. Therefore, information on possibly altered THC PK characteristics (e.g. systemic availability) when coadministered with CBD is important for dosing optimisation. Also PK studies of vapourised CBD are very limited and a corresponding PK model was not found in the literature [13]. In addition, as some patients using cannabinoids medically are also intermittently using cannabis recreationally, prescribers need to be aware of any difference in the PK of cannabinoids in both cannabis naïve and regular users in order to determine optimum dosing for these groups.

The aims of this study were to: 1) investigate the influence of coadministered CBD on the systemic availability of THC in different drug conditions based on the developed THC population PK model; 2) develop a population PK model for vapourised CBD; and 3) compare and contrast the systemic availability of THC, as well as CBD in a sample of frequent and infrequent cannabis users.

METHODS

Study Design
This study used a randomised, double-blind, crossover placebo-controlled design. Each subject participated in the 5 drug conditions of the study, as depicted in Table 1. A minimum of one week wash out period between drug conditions was applied.

Drugs
THC and CBD were dissolved in an ethanolic solution, 4% for THC and 10% for CBD, while the 100% ethanol vehicle served as the placebo (all purchased from STI Pharmaceuticals, Essex, UK). The THC+low CBD dose was selected to emulate the proportions found in some strains of cannabis plant matter [14], while the high dose CBD was chosen to be similar to that administered orally in other studies that showed therapeutic benefits [15] or activation of brain circuitry [16]. Further rationale for the dosing regimen has been described in our paper reporting first outcomes from this overall study [17].
Dose and drug delivery

The drug solution (containing THC and/or CBD in ethanol) was vaporised via a Volcano® Vaporiser (Storz & Bickel GmbH & Co. Tuttlingen, Germany) into a Volcano® Easy Valve balloon immediately prior to inhalation by the participant. Table 1 shows the doses loaded into the vaporiser; the actual dose vaporised and available in the balloon for patients’ inhalation was smaller due to saturation and inefficiencies inherent in the vaporisation process (80% for THC, 97.5% for low dose CBD and 40% for high dose CBD; see reference [18]).

Drug administration

In total, three doses in sequence were given to each participant for each drug condition, i.e. main dose and 2 top-up doses as in Table 1. Each participant was first administered the main dose, via two normal sized Volcano® Easy Valve balloons. The balloon was covered by opaque fabric to prevent identification of vapour colour or density. Participants were instructed to inhale a comfortable amount and hold their breath for 10 seconds before exhaling. Drug administration for the main dose took approximately 10 minutes, involving 6-10 inhalations from each balloon. Approximately 60 min later, the first of two top-up doses were administered with a further hour interval prior to the second top-up dose, as shown in the schematic of Figure 1. Top up doses were administered for the purposes of maintaining intoxication throughout an experimental trial [ISRCTN24109245] [17]. Top-up doses were vaporised into and delivered in a single balloon. However, not all participants were able to intake all three doses or inhale all of the contents of each of the four balloons due to becoming too intoxicated or finding the vaporised compounds irritating to the throat. In addition, blood samples were not available from all participants for all 5 conditions. The exact number of participants from whom blood samples were obtained in each drug condition is presented in the “Results” section.

Sampling

Venous blood was collected via a cannula. To monitor plasma concentrations of THC and CBD and metabolites of THC, blood samples were taken prior to vaporisation of the first balloon of the main dose, and then at approximately 10, 20, 40, 60 minutes after inhalation of the two balloons comprising the main dose, as shown in Figure 1.

Participants

Participants were interviewed before the trial and required to have used cannabis at least 5 times, with the constraint that less experienced users (5 to 10 lifetime uses) must have used at least once in the past 2 years. Participant who reported having used a substance other than cannabis, alcohol or tobacco in the two weeks prior to testing or provided a positive urine drug screen was omitted from the study. Participants with neurological or other substance use disorders, head injury, cardiovascular disease, untreated hypertension or previous adverse reactions to cannabis were excluded.
Participants were grouped on the basis of median split on lifetime use of cannabis, into frequent users (133 ~ 8000 lifetime occasions, with median 307 occasions) and infrequent users/non-naïve nonusers (6 ~ 123 lifetime occasions, with median 24 occasions). Detailed drug use history and categorization method for participants were described in our previous publication [17]. Of note, infrequent users/non-naïve nonusers henceforth are referred to as infrequent users.

For each session, participants remained in the laboratory for at least 3 hours after administration of the last top-up dose and/or until intoxication ratings had returned to pre-baseline levels. They were transported to their home in a taxi and advised not to drive for the remainder of the day.

The study was approved by the University of Wollongong and Illawarra and Shoalhaven Local Health District Health and Medical Human Research Ethics Committee. Participants provided written informed consent prior to every session and were free to withdraw from the study at any time.

Whole Blood Analysis

Blood (5 ml) was collected into EDTA tubes and centrifuged at 2000 x g for 10 min at 4°C. Plasma was separated and kept at -80°C until analysis. Plasma samples were thawed and 50µl were added to 100µL of acetonitrile containing deuterated internal standards. The samples were vortexed then centrifuged and the supernatant was transferred to a vial and injected onto the LCMS system (Shimadzu 8060). A Kinetex Biphenyl column (50 x 3mm, 2.6µm) using a gradient of 0.1% formic acid and acetonitrile was used for the analysis. Concentrations of THC and CBD were measured.

Data

Most of the blood samples for measuring THC concentrations were collected within 1 hour after the main dose as depicted in Figure 1. These samples cover the distribution phase of THC, considering the reported relatively long half-life (~ 20 hours) in elimination phase of THC [12, 19]. Therefore, a population PK model of THC appropriately describing its PK profile based only on the available THC concentrations is not possible. Ohlsson et al. [19] reported PK data from 5mg THC administered intravenously and in smoked cannabis containing 10mg THC in 9 healthy male subjects with 151 blood samples drawn for up to 48~72 hours after administration, covering properly the elimination phase of THC. In this analysis, our data of measured THC plasma concentrations by vaporised route (i.e. conditions of THC, THC+low-dose CBD and THC+high-dose CBD in Table 1) were pooled together with Ohlsson’s data. Resultantly, the missing information in the elimination phase of THC in our data can be provided by Ohlsson’s data.

For the pure CBD condition in our study, again most of the blood samples were also collected within 1 hour after the main dose, providing information only on the distribution phase and...
not the elimination phase. Ohlsson et al. [20] reported PK data for CBD from intravenous infusion of 20mg CBD and in smoked cannabis containing 20mg of CBD in 5 healthy male subjects with 139 blood samples drawn for up to 48–72 hours after administration, covering the anticipated elimination phase of CBD. However, the CBD plasma concentrations were reported in terms of mean±S.D. and range, rather than individual participant data. This makes the use of Ohlsson’s data difficult for model development. Resultantly, the parameter of clearance of CBD in the elimination phase was fixed to the value reported by Ohlsson during the parameter estimation process in our analysis.

Data Analysis

NONMEM Version 7.2.0 [21] in combination with the gfortran compiler, PsN (Perl-speaks-NONMEM) version 4.7.0 [22,23], PLT tool [24], and R Version i386 3.3.1 [25] were used for model development and graphical illustration. Parameter estimation was conducted with the first-order conditional estimation with interaction (FOCE+I). Both 2- and 3- compartment models for THC or CBD were tested. Different error models including additive, proportional and combined error models were tested to describe the residual unexplained variability (RUV). Inter-individual variability (IIV) as an exponential relationship was tested on each pharmacokinetic parameter. The off-diagonal elements, representing the covariance of IIVs were tested. The reduction of the objective function value (OFV), conditional weighted residuals (CWRES) versus time after dose for THC or CBD and prediction-corrected and variance-corrected visual predictive checks (pcvcVPC) were used as diagnostics and to judge the goodness of fit [26]. 95% bootstrap (i.e. a common method to validate nonlinear mixed effects models) confidence intervals for the final population model parameters were conducted using PLT tools with subject replacement of 500 runs [27].

RESULTS

Demographics

There were 36 participants recruited for this study and 18 participants were categorised into each of the frequent and infrequent cannabis user groups. The demographic information is presented in Table 2.

Blood samples were not available in some participants due to difficulties with the cannula and blood flow on certain days. As such, participant numbers with available blood samples were 34 (16 frequent users/18 infrequent users), 30 (16/14), 31(16/15) and 31(16/15) for the THC, CBD, THC+low-dose CBD and THC+high-dose CBD conditions respectively.

Model development

Details of the models and their validation are in Supplement 1 and 2 respectively. NONMEM control streams are in Supplement 3. Model parameters are presented in Table 3 and 4.
Systemic availability of THC in different drug conditions

The systemic availability of THC decreased significantly once high dose CBD was given simultaneously, $F(\text{THC+high-dose CBD})=0.22$ compared to $F(\text{THC})=0.50$ as in Table 3. However, the low dose CBD did not affect the availability of THC, $F(\text{THC+low-dose CBD})=0.58$.

Systemic availability in Frequent and Infrequent users

The estimated categorisation covariate parameter value (i.e. to investigate the difference in systemic availability between the frequent and infrequent users) indicated similar availability for THC alone and THC+low-dose CBD (Table 3) (1.09 and 0.93 are both close to 1.0). However, the parameter values of 1.28 in the THC+high-dose CBD condition (Table 3) and 1.26 in the CBD alone condition (Table 4) (both perceptibly larger than 1.0), suggest that frequent users may have higher systemic availability of THC than infrequent users in the presence of high dose CBD, and higher systemic availability of CBD when high-dose CBD is administered alone.
DISCUSSION

One aim of this study was to investigate the influence of coadministered CBD at low and high doses on the systemic availability of THC based on the developed THC population PK model. The term systemic availability is often customarily used interchangeably with bioavailability when they both refer to the total amount of drug that eventually reaches the systemic circulation from a certain dose. For bioavailability, the lost proportion of a dose is due to the drug passing all hurdles in the biological system, e.g. first pass effect. For systemic availability, the lost proportion of a dose is due to not only loss in the biological system, but also loss before and during the drug delivery. With vaporisation this loss may occur due to saturation effects in the vapour (i.e., incomplete vaporisation), different sized particles adhering at different points in the respiratory system (i.e. not being absorbed efficiently) and cannabinoids being exhaled after breath holding [10, 28]. Therefore, the term systemic availability is used in this paper. Also notably, the systemic availability in this study is an apparent value instead of an absolute value. This is because absolute availability can only be determined in a crossover study design with an IV administration arm, combined with, for example, inhalation or oral arms. Here we had to rely on IV data from Ohlsson et al [19] to enable population PK modelling.

It can be seen from Table 3 that the systemic availability, $F(\text{THC+high-dose CBD}) = 0.22$ is significantly lower than $F(\text{THC}) = 0.50$, and $F(\text{THC+low-dose CBD}) = 0.58$. One reason is that high dose CBD, as an irritating component in vapor form [18], hindered the participants from consuming the whole dose. Resultantly, the systemic availability of THC coadministered with high dose CBD decreased significantly. Since the modelling exercise incorporates THC exposure in the systemic availability $F$, the difference in $F$ is based on different THC exposure of different drug conditions in the raw data. This indicates that THC exposure in the THC+high-dose CBD is significantly lower than in the THC alone or THC+low-dose CBD conditions. Noticeably, we don’t recommend giving high dose CBD alone or together with THC by vaporization, due to its high irritability. In such case, clinicians may prefer to use an oral route of CBD, in order to avoid the irritability. However, low-dose CBD, either alone, or combined with THC, emulates plant matter and could be applied therapeutically. Irritation to the throat was far less in this condition.

On comparing the systemic availability in the different user groups, the estimated categorisation covariate parameter value in the THC+high-dose CBD condition (1.28 in Table 3), is larger than 1.0. This indicates that frequent cannabis users might have higher systemic availability (or exposure) of THC than infrequent users in the presence of high dose CBD. Also the systemic availability in frequent users of CBD when administered alone is higher than infrequent users (the estimated categorisation covariate parameter value is 1.26 as in Table 4). However, frequent and infrequent users have similar availability in the THC alone and THC+low-dose CBD conditions with the parameter values 1.09 and 0.93 respectively (close to 1.0). This is possibly because frequent users have better tolerability of the irritating effects of high dose vaporised CBD (i.e. THC+high-dose CBD and CBD alone conditions) on the throat than the infrequent users, and hence consumed more of the vapours from the
balloon in this condition. Indeed, our observations on the consumed drug proportion (Supplement 4) support this interpretation.

The parameters estimated with bootstrap for the THC model in this study produced similar parameter values to those in the final model (Table 3), suggesting that the estimated parameter values in the final model are robust and reliable. Notably, the THC PK model developed in this work describes the full THC PK profile, especially the long terminal phase of THC. Therefore, this model can be used in multiple dose planning because it considers the drug accumulation issue, likely to be relevant in patients taking daily doses of medical cannabinoids.

For the developed CBD model, some of the bootstrap parameters (Table 4) have relatively large 95% CIs, indicating issues with the parameter identification. This is an evident limitation of the model and most likely because our CBD data contain relatively limited information to perfectly identify all the model parameters. However, the model as developed is able to describe the observations appropriately and is an important addition to this field as no CBD PK models are currently available in the literature [13].

CONCLUSION

In this study, population pharmacokinetic models of THC and CBD after vaporised administration were developed. The THC PK model suggests that the systemic availability of THC decreases when high dose CBD is given simultaneously. In addition, frequent cannabis users appear to have higher systemic availability of THC in the presence of high dose CBD, and of CBD when administered alone, than infrequent users.

Authors’ contributions Samantha J Broyd, Hendrika van Hell and Lisa-marie Greenwood conducted the original study (e.g. data collection and participant management) in the lab of Nadia Solowij. Zheng Liu developed the models, analysed the data, prepared the figures and tables, and drafted the first manuscript. Peter Galettis developed and validated the assay and analysed the blood samples. Peter de Krey and Amy Steigler assisted with analysing the blood samples. Xiao Zhu contributed to data analysis. Jennifer Schneider contributed to data analysis. Jennifer Martin oversaw the PK analysis, checked the data, planned the write up and edited the manuscript. All reviewed the data and contributed to the writing of the manuscript.

Funding Supported by the National Health and Medical Research Council (NHMRC Centre of Research Excellence – Australian Centre of Cannabinoid Clinical and Research Excellence; Martin, Solowij APP1135054); (NHMRC Project Grant; Solowij, APP1007593); the Australian Research Council (ARC Future Fellowship; Solowij FT110100752).

Compliance with ethical standards The study was approved by the University of Wollongong and Illawarra and Shoalhaven Local Health District Health and Medical Human Research Ethics Committee.
Conflict of interest The authors have no conflicts of interest to report.

REFERENCES


Table 1. The five randomised drug conditions: Placebo; THC; CBD; THC+low-dose CBD; THC+high-dose CBD

<table>
<thead>
<tr>
<th>Drug conditions</th>
<th>Main Dose (balloon 1)</th>
<th>Main Dose (balloon 2)</th>
<th>Top-Up-Dose-1</th>
<th>Top-Up-Dose-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>THC (mg)</td>
<td>CBD (mg)</td>
<td>THC (mg)</td>
<td>CBD (mg)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>THC</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CBD</td>
<td>0</td>
<td>200</td>
<td>0</td>
<td>200</td>
</tr>
<tr>
<td>THC+low-dose CBD</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>THC+high-dose CBD</td>
<td>8</td>
<td>200</td>
<td>4</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Frequent users</td>
<td>Infrequent users</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
<td>------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>21.8 [19.41-44.6]</td>
<td>20.5 [18.9-51.1]</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Gender [male:female]</td>
<td>[17:1]</td>
<td>[14:4]</td>
<td>0.169</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 [46-108]</td>
<td>72 [53-103]</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>183 [168-193]</td>
<td>180 [150-187]</td>
<td>0.0571</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 [16-33]</td>
<td>22 [19-31]</td>
<td>0.159</td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>15 [10.0-18.0]</td>
<td>14 [11.5-16]</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>IQ</td>
<td>115.5 [104-131]</td>
<td>117.5 [102-129]</td>
<td>0.927</td>
<td></td>
</tr>
<tr>
<td>Tobacco frequency (days/month)</td>
<td>2.1 [0.0-30.0]</td>
<td>1.3 [0.0-30.0]</td>
<td>0.628</td>
<td></td>
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<tr>
<td>Tobacco quantity (cigarettes/occasion)</td>
<td>1 [0.0-20.0]</td>
<td>1.1 [0.0-11.0]</td>
<td>0.791</td>
<td></td>
</tr>
<tr>
<td>Alcohol frequency (days/month)</td>
<td>9 [2.0-15.8]</td>
<td>4.5 [5.5-9.0]</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Alcohol quantity (drinks/occasion)</td>
<td>10 [3.5-20.0]</td>
<td>9 [1.4-20.0]</td>
<td>0.628</td>
<td></td>
</tr>
<tr>
<td>Cannabis use Frequency (days / month)</td>
<td>10 [2.3-27.5]</td>
<td>0 [0.0-5.0]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cannabis use Quantity (cones* / month)</td>
<td>37 [11.6-341.6]</td>
<td>3.38 [0.0-24.8]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age of first use (years)</td>
<td>16.25 [14.0-19.0]</td>
<td>18 [15.0-28.0]</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Lifetime use (no. occasions)</td>
<td>307.22 [133.0-7988.9]</td>
<td>24.35 [6.0-123.1]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Use past year (no. occasions)</td>
<td>120 [27.0-330.0]</td>
<td>12 [0-60]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Use past month (no. occasions)</td>
<td>9 [1.0-28.0]</td>
<td>1.5 [0.0-8.0]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Duration of regular use (years)*</td>
<td>2.91 [1.4-25.5]</td>
<td>1.58 [0.5-4.5]</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>Time since last smoked (hours)</td>
<td>31 [12.5-456.0]</td>
<td>336 [39.0-157680.0]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Notes: a Cones used in waterpipe; 3 cones are equivalent to one standard sized joint; b Duration of regular use in regular users only
Table 3. Estimated parameter values and bootstrap results for the final THC model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Parameter estimate</th>
<th>Infrequent v.s. Frequent</th>
<th>BSV % [shrinkage]</th>
<th>Bootstrap (median [95% CI])</th>
<th>Parameter estimate</th>
<th>Infrequent v.s. Frequent</th>
<th>BSV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>L</td>
<td>6.15 FIXED</td>
<td>-</td>
<td>50.0 [14.2%]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>48.3  [40.0-59.1]</td>
</tr>
<tr>
<td>V2</td>
<td>L</td>
<td>184.8</td>
<td>-</td>
<td>-</td>
<td>183.0 [154.2-217.6]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V3</td>
<td>L</td>
<td>25.6</td>
<td>-</td>
<td>-</td>
<td>25.4 [17.5-34.5]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CL</td>
<td>L/h</td>
<td>37.7</td>
<td>-</td>
<td>29.0 [16.8%]</td>
<td>37.1 [25.4-48.6]</td>
<td>-</td>
<td>-</td>
<td>29.5  [25.7-34.0]</td>
</tr>
<tr>
<td>Q1</td>
<td>L/h</td>
<td>7.2</td>
<td>-</td>
<td>-</td>
<td>7.8 [4.9-10.4]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Q2</td>
<td>L/h</td>
<td>27.7</td>
<td>-</td>
<td>-</td>
<td>27.3 [17.0-37.5]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F (smoking)*</td>
<td>-</td>
<td>0.22</td>
<td>-</td>
<td>-</td>
<td>0.21 [0.14-0.27]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F (THC)</td>
<td>-</td>
<td>0.50</td>
<td>1.09 (SD=0.15)**</td>
<td>21.7 [37.3%]</td>
<td>0.52 [0.42-0.60]</td>
<td>1.06 [0.70-1.30]</td>
<td>24.3 [15.6-32.1]</td>
<td>-</td>
</tr>
<tr>
<td>F (THC+low-dose CBD)</td>
<td>-</td>
<td>0.58</td>
<td>0.93 (SD=0.16)**</td>
<td>50.0 [6.9%]</td>
<td>0.56 [0.47-0.65]</td>
<td>0.96 [0.64-1.27]</td>
<td>48.5 [40.7-57.6]</td>
<td>-</td>
</tr>
<tr>
<td>F (THC+high-dose CBD)</td>
<td>-</td>
<td>0.22</td>
<td>1.28 (SD=0.24)**</td>
<td>38.5 [15.5%]</td>
<td>0.22 [0.10-0.33]</td>
<td>1.31 [0.84-1.78]</td>
<td>36.5 [24.7-50.3]</td>
<td>-</td>
</tr>
</tbody>
</table>

Residual error
proportional (Ohlsson data) % 31.4 - - 34.1 [29.1-39.0] - -
additive (Ohlsson data) ng/ml 0.02 - - 0.03 [0.01-0.04] - -
proportional (vaporised data) % 28.5 - - 28.3 [23.8-32.7] - -

* F(smoking) is the systemic availability of smoked route from Ohlsson’s data.
** The categorisation covariate model is as F = θinfreq * θfreq * GROUP, where GROUP = 0 and 1 represent Infrequent and Frequent users respectively. E.g. for the THC+high-dose CBD condition, θfreq = 1.28 indicates that the systemic availability of Frequent users is 1.28 times of the Infrequent users.
Table 4. Estimated parameter values and bootstrap results for the final CBD model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Parameter estimate</th>
<th>Infrequent v.s. Frequent</th>
<th>BSV % [shrinkage]</th>
<th>Bootstrap (median [95% CI])</th>
<th>Parameter estimate</th>
<th>Infrequent v.s. Frequent</th>
<th>BSV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1/F</td>
<td>L</td>
<td>66.1</td>
<td>-</td>
<td>-</td>
<td>63.8 [9.1-109.5]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V2/F</td>
<td>L</td>
<td>1570.7</td>
<td>-</td>
<td>-</td>
<td>1520.4 [543.8-2535.7]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CL/F</td>
<td>L/h</td>
<td>74.4 FIXED</td>
<td>-</td>
<td>49.9 [%]</td>
<td>1520.4 [543.8-2535.7]</td>
<td>-</td>
<td>-</td>
<td>48.3  [40.0-59.1]</td>
</tr>
<tr>
<td>Q1/F</td>
<td>L/h</td>
<td>370.6</td>
<td>-</td>
<td>-</td>
<td>376.1 [12.5-709.5]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>0.50</td>
<td>1.26 (SD=0.14)*</td>
<td>26.3 [%]</td>
<td>0.51 [0.14-0.83]</td>
<td>1.23 [1.0-1.47]</td>
<td>24.5 [10.7-28.1]</td>
<td></td>
</tr>
</tbody>
</table>

Residual error
proportional

* The categorisation covariate model is as $F = \theta_{infreq} \times \theta_{freq} \times \text{GROUP}$, where GROUP = 0 and 1 represent Infrequent and Frequent users respectively. $\theta_{freq} = 1.26$ indicates that the systemic availability of Frequent users is 1.26 times of the Infrequent users.
Figure. 1 Dosing and sampling for all drug conditions