Clin Pharmacokinet (2015) 54:129–131
DOI 10.1007/s40262-014-0210-x

COMMENTARY

Toward a Comprehensive Model of Δ^9-Tetrahydrocannabinol Pharmacokinetics Using a Population Pharmacokinetics Approach

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Published online: 7 November 2014

1 Introduction

In the article "Population pharmacokinetic model of THC integrates oral, intravenous, and pulmonary dosing and characterizes short- and long-term pharmacokinetics", Heuberger and colleagues [1] describe a model of Δ^9-tetrahydrocannabinol (THC) pharmacokinetics derived from a population pharmacokinetics approach. Population pharmacokinetics is an analytical strategy that develops a statistical model describing the functional relationship between the concentration of a drug and time, typically using non-linear regression with data from individual subjects [2]. A major advantage of this approach over more traditional methods is that the model can be derived from sparsely sampled clinical data, requiring only a few samples from each subject [2, 3]. Further, the data can come from distinct studies with different experimental designs [2]. Population pharmacokinetics is often used to identify pharmacokinetic differences between populations of interest (e.g., adults vs. children). However, the model can also be used to characterize pharmacokinetics of different routes of administration, while still accounting for individual differences in drug disposition [3]. These features can produce detailed models that are relevant to clinical applications (e.g., by guiding a dosing strategy that maintains a drug's concentration within its therapeutic range) [2].

The model developed by Heuberger and colleagues could improve the therapeutic use of THC, which is under consideration for an expanding range of maladies [4–6]. The pharmacokinetics of THC are complex, and depend on the route of administration as well as individual subject factors such as metabolic capacity and adiposity [7]. This variability, along with the challenge of obtaining repeated samples in an individual over the extended duration required to capture THC elimination, poses a challenge to the development of a comprehensive model of THC pharmacokinetics. The population pharmacokinetic approach used by Heuberger and colleagues [1] addresses these challenges. The model the authors developed used historical data from four different datasets that included pulmonary (either smoked or vaporized), intravenous, and oral routes of administration. The model was then validated by performing visual predictive checks with data not used to build the model. This validation is an important aspect of the work and increases confidence that the model can be generalized to other studies, and, ultimately, to clinical applications. Notably, the model of Heuberger and colleagues (1) incorporates various routes of administration, (2) allows blood THC concentration estimates for an individual from relatively few samples, and (3) incorporates the long terminal phase of THC elimination. Below, the implications of these features are discussed, followed by a description of areas requiring additional research before the model can be applied clinically.

2 Strengths and Implications of the Population Pharmacokinetics Model of Δ^9-Tetrahydrocannabinol (THC)

One strength of the model Heuberger and colleagues describe is that it accounts for different routes of administration. Smoking remains the primary route of cannabis administration [8]. However, recognition that smoking is undesirable has resulted in a variety of alternative routes, even among recreational users [7–9]. These alternatives to smoking include

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vaporization and oral delivery. Vaporizers heat the plant material to about 185 °C; hot enough to vaporize the volatile cannabinoids (which are then inhaled), but not hot enough to induce combustion [10]. THC-infused edible products and other oral formulations are also available, and at least one company has developed an oral-mucosal cannabis extract spray [11]. These routes have different applications, particularly when used therapeutically. Accommodating them extends the utility of this model, allowing its use regardless of which of these routes of administration the patient and his or her healthcare provider determine is optimal.

The model can also estimate THC blood concentrations achieved at various times after the most recent dose administered. Even when cannabis administration is carefully controlled, the peak blood THC concentration produced by a particular dose is highly variable across individuals [12], probably due to still poorly understood factors such as diet and exercise [13, 14]. This variability complicates predicting the blood THC concentration at a particular timepoint after a given dose in an individual. However, with this model, by collecting as few as two samples from an individual within 48-h after THC administration, the blood concentration achieved by that dose can be estimated at any timepoint since it was administered. This could help individualize treatment and ensure that therapeutic concentrations of THC are achieved and maintained.

Finally, incorporating the long terminal phase of THC elimination from blood into this model is important. Estimating THC blood concentration during the long terminal phase is complicated by sequestration and leaching of THC from fat stores [15]. This terminal portion of the THC pharmacokinetic curve has been less studied than earlier portions of the curve, in part due to the difficulty of quantifying the low THC concentrations present during this period [7]. Because the dataset the authors used for this terminal portion is relatively small and may not be optimal for the complex model Heuberger et al. developed [16], additional data could lead to refinement of the model. Still, the model described by Heuberger et al. [1] characterizes the long terminal phase of THC elimination which begins about 10-h after administration. The model could thus estimate when blood THC concentrations are likely to fall below a particular therapeutic threshold. This could help treatment providers determine the optimal time between doses, especially when the inter-dosing interval exceeds 10 h.

3 Research Needed for Clinical Application of the Population Pharmacokinetics Model of THC

Despite the advance this study represents, several knowledge gaps must be filled before blood THC pharmacokinetics are useful in guiding pharmacotherapy. First, this model only addresses the pharmacokinetics of a single compound found in cannabis, and does not include other active constituents in cannabis or synthetic cannabinoids. Additionally, the relationship between blood and target organ THC concentrations are complicated and poorly understood. Further, effective therapeutic THC concentrations have yet to be established. These aspects are discussed below.

The model developed by Heuberger and colleagues only addresses the pharmacokinetics of a single compound found in cannabis, THC. THC is one of dozens of cannabinoids present in cannabis [17]. These other constituents can also exert pharmacological effects and interact with THC. For example, there is evidence that cannabidiol (another cannabinoid constituent of cannabis) can modify the effects of THC, and may itself provide therapeutic benefit for epilepsy [18]. Thus, this model is far from a complete representation of the pharmacokinetics of cannabis or extracts containing multiple constituents.

Similarly, this model does not address the pharmacokinetics of synthetic cannabinoids. Synthetic cannabinoids are under active development as therapeutics and also represent a growing substance abuse problem [19]. These drugs have different pharmacological and pharmacokinetic profiles compared with THC [19, 20]. Thus, this model does not address other drugs similar to THC that are clinically relevant.

Another limitation of the model arises because the relationship between THC concentration in blood and THC concentration in various target organs remains unclear. A sizable literature demonstrates that blood THC concentrations do not predict behavioral effects (e.g., [21, 22]). This is likely because THC must leave the blood and contact cannabinoid receptors in the brain to exert its behavioral effects. THC penetration into the brain appears to be rate-limited, with maximal concentrations in the brain lagging 2–4 h after maximal blood concentrations are achieved [23]. This results in poor correlation between the concentration of THC in blood and brain [24]. Similar differences between THC pharmacokinetics in blood versus other organs have also been described [23]. In most cases, the target for THC pharmacotherapy will not be in the blood, but rather in the brain or other organs; thus, this model provides limited guidance on achieving optimal THC concentrations at the site of action of interest.

Further, even if we could predict concentrations of THC in various target organs, effective therapeutic THC concentrations have not yet been established. Presently, the effectiveness of THC is being evaluated for a wide range of maladies. Determining the optimum THC concentration at the site of action for each of these situations will require further study. Once the pharmacokinetics and optimum concentration of THC at the target site of action are clear,

the full potential of pharmacokinetic models of THC can be realized for a particular therapeutic application.

4 Conclusions

In conclusion, the model described by Heuberger et al. incorporates multiple routes of administration and better describes the long terminal phase of THC elimination, which could help guide pharmacotherapy with cannabis or THC. However, application of this model is limited by several issues that will require further study. These limitations include the lack of inclusion of other constituents in cannabis or synthetic cannabinoids, the lack of correspondence between concentrations of THC in the blood and other organs, and the lack of evidence for effective THC concentrations in various therapeutic applications. Despite these limitations, Heuberger et al. provide a valuable step towards improving therapeutic use of THC.

Acknowledgments The author has no conflicts of interest to declare. This work was funded by the Department of Psychiatry, The University of Texas Health Science Center at San Antonio.

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