Population PK Model of THC Integrates Oral, Intravenous and Pulmonary Dosing and Characterizes Short and Long Term PK

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INTRODUCTION

Δ^9-Tetrahydrocannobinol (THC), the main psychoactive compound of cannabis, is known to have a long terminal half-life. However, this characteristic is often ignored in pharmacokinetic (PK) studies of THC, which may affect the accuracy of predictions in different pharmacologic areas.

AIM

To develop a multi-compartment population PK model for THC using clinical data, incorporating the terminal phase of THC and the three most important administration routes (oral (PO), intravenous (IV) and pulmonary (IP)) in order to improve simulations and predictions of THC concentrations in therapeutic and clinical research settings.

METHODS

The PK model was developed using NONMEM® 7.2. Datasets were obtained from a cross-over study with a single dose (9 mg pulmonary and 4.55 mg IV)[1], two multiple dose studies (2, 4, 6 mg / 2, 6, 6 mg pulmonary, 1.5 h interval)[2,3] and a single dose study (5, 6.5 or 8 mg PO of Namisol®)[4]. During the multiple dose studies, subjects wore a nose-clip to prevent exhalation through the nose.

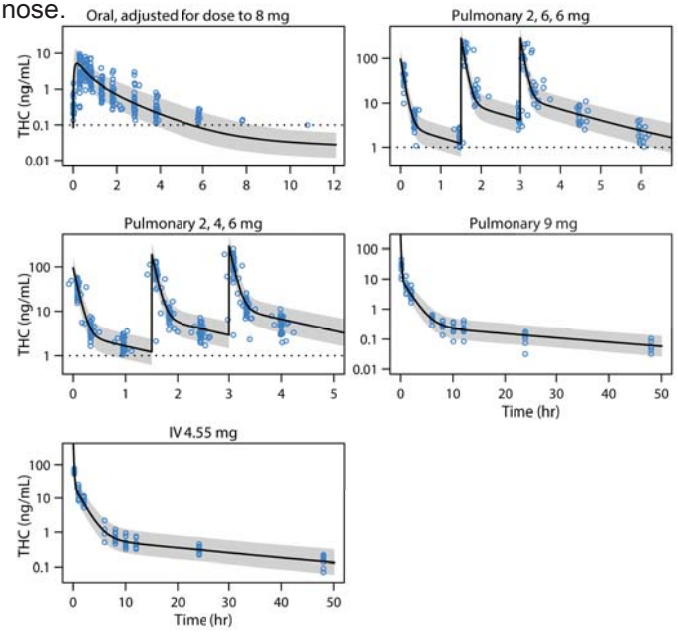

Figure 1: Visual Predictive Checks. Blue circles: observations; Black line, typical predicted concentration; Gray area, 95% prediction interval; Dotted line, limit of quantification.

RESULTS

The final three-compartment model shows that THC has a fast initial and intermediate half-life, while the apparent terminal half-life is long (21.5 hrs), with a clearance of 38.8 L/h and estimated apparent absorption fractions of 2.4-4.1%, 25.1-34.0% and 18.4-27.8% (95% confidence intervals) following PO, IP with and without a nose clip, respectively. Data were collected from 84 subjects (18 female), with a mean age of 22 yrs and BMI of 22.4 kg/m^2.

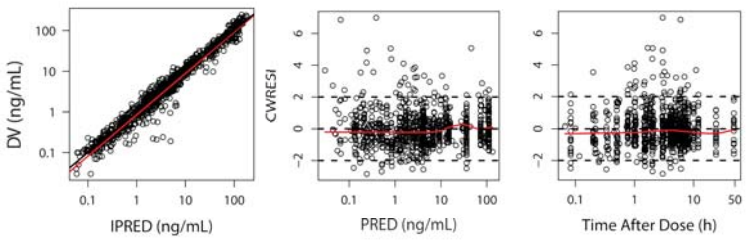

Figure 2: Diagnostic plots, red line is a regression (left) or LOESS line (middle and right, span=0.75) through the observations.

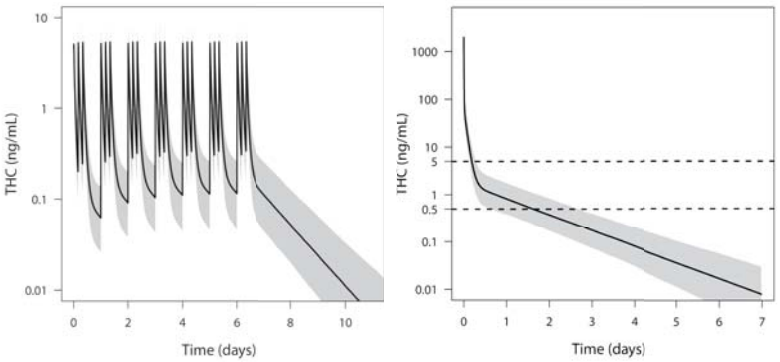

Figure 3: Simulations of (left) a trial 8 mg oral TID for 7 days and (right) a single IP 54 mg marijuana cigarette (typical dose). Black line, typical predicted concentration; Gray area, 95% prediction interval; Dashed line, intoxication level (5 ng/mL) and detection level (0.5 ng/mL) in plasma.

CONCLUSIONS

This PK model accurately describes:

- Long terminal half-life of THC
- Three major administration routes
- Accumulation of THC

Can be used for:

- Improved trial design in THC drug development
- Better use of the THC challenge test

Poster copy

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[2]Kleinloog D, Liem-Moolenaar M, Jacobs G, Klaassen E, de KM, Hijman R et al. Does olanzapine inhibit the psychomimetic effects of Delta(9)-tetrahydrocannabinol? J Psychopharmacol 2012; 26:1307-1316.
[3]Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Single dose kinetics of deuterium labelled delta 1-tetrahydrocannabinol in heavy and light cannabis users. Biomed Mass Spectrom 1982; 9:6-10.
[4] Klumpers LE, Beumer TL, van Hasselt JG, Lipplaa A, Karger LB, Kleinloog HD et al. Novel Delta(9) -tetrahydrocannabinol formulation Namisol(R) has beneficial pharmacokinetics and promising pharmacodynamic effects. Br J Clin Pharmacol 2012; 74(1): 42–53

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