Evaluation of the Short-term Clearance of Perflourooctanoic Acid (PFOA) in a Clinical Trial Using a PBPK Model and Markov Chain Monte Carlo Analysis

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Abstract

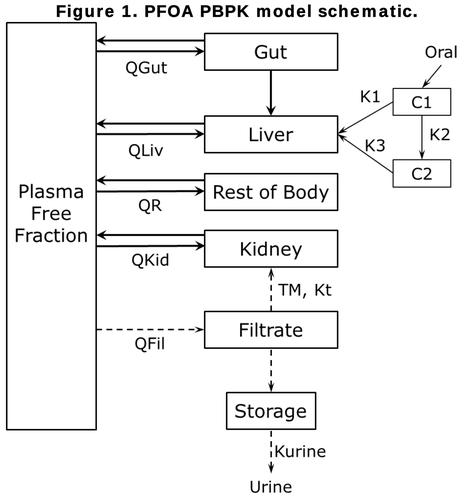
Several studies have estimated a terminal half-life for the urinary clearance of perfluorooctanoic acid (PFOA) in the range of 2-4 years; however, the short-term clearance of PFOA has not been previously reported. In this study, single- and repeated-dose pharmacokinetic data from a human clinical trial with 50 patients being treated for cancer (CXR database) was analyzed using a physiologically based pharmacokinetic (PBPK) model in a Markov chain Monte Carlo (MCMC) analysis. The MCMC approach allowed for incorporation of prior knowledge about PFOA kinetics and a hierarchical structure accounting for inter-individual variability. The median age of the patients in the trial was 63 with a minimum of 36 and maximum of 74. The half-life in these patients had a mean of 0.13 yrs with a range of 0.013 to 0.8 yrs, significantly shorter than estimates of the terminal half-life derived from chronic exposures. The relationship of PFOA dose and AUC was not suggestive of a significant departure from linearity for doses ranging from 50 to 1200 mg/day for up to 6 weeks. Only a small portion of the variance in AUC was accounted for by GFR, suggesting that filtration is not as influential as reabsorption in the short-term clearance of PFOA. Based on this finding, the calibration was designed to refine the most sensitive parameters in the model, including the maximum velocity and affinity constant for renal resorption and the free fraction in plasma.

Introduction

A significant uncertainty identified during the development of the human PFOA model (Loccisano et al., 2012) was the existence of divergent estimates of the human half-life for PFOA. While kinetic data are available to support estimation of the half-life in experimental species, the data for humans are much less certain. The principal half-life studies in humans was an assessment based on the decrease in serum concentration in retired workers (Olsen et al, 2007) and two samples collected from a population before and after upgrades to the water treatment to remove PFOA from drinking water supply Bartell et al., 2010). The resulting half-life estimates from these studies was 3.8 years (95% CI: 3.1–4.4 years) and 2.3 years, respectively; however both studies had confounding issues that may have skewed the estimated half-life.

This effort focuses on using plasma and urine data from a control human clinical trial study to calibrate the adult human PFOA model. A formal calibration would center on the use of a Bayesian approach known as Markov Chain Monte Carlo (MCMC) where information from prior distributions of model parameters and fit of the model to the selected data sets is combined in a hierarchical Bayesian framework to generate posterior distributions for parameters reflecting both uncertainty and variability. The posterior distributions for both the model parameters and the estimated half-lives will provide a valuable resource for characterizing the human interindividual variation in the pharmacokinetics of PFOA.

Figure 1. PFOA PBPK model schematic.



Methods

PFOA PBPK Model

- Loccisano et al. (2011) adult human model modified to fit the time-course shape of the 50 mg dose in CXR database
- 2 compartment pseudo intestinal model used for oral uptake
- TMC, KT, KURINEC were visually to fit the plasma and urine from CXR clinical trial - mean value used for calibration
- Fractional blood flows were constrained to unity by dividing the fractional blood flow for each tissue by the sum of all fractional blood flows
- Tissue volumes were constrained to sum to 86% BW representing perfused tissue

CXR Clinical Database

- Primary objective to determine the safety, toxicity, dose limiting toxicity (DLT), and maximum tolerated dose (MTD) of CXR 1002
- Male and female patients with advanced solid tumors that are refractory to standard therapy or no standard therapy exists
- Six weekly oral doses of 50, 150, 200, 300, 450, 650, 750, 950, or 1000 mg with 3 patients administered a single 50 mg or dose
- Plasma conc. measured at 2, 3, 4, 24, and pre-dose each week
- 24 hour urine collected weekly on day of dosing for 650 mg (1 patient) to 1000 mg (12 patients) dose groups.

Markov Chain Monte Carlo Analysis

- MCMC analysis performed using MCSim (ver. 5.6.4, Bois, et al., 2002) with diagnostics assess using Coda (ver. 0.18) in R (ver. 0.99.878)
- Parameters with means and variances updated chosen for their sensitivity to plasma concentration, mass excreted in urine
- Boundary values set to ± 2.5 SD to facilitate convergence
- FracFil (fraction kidney perfusion filtered) was given a uniform distribution for the prior mean and truncated between 0.2 and 1.0 to test if the data were informative for active secretion in the kidney (i.e., posterior mean >>0.2 would indicate active secretion)
- Parameters that were updated (means and variance) were log transformed and sampled with truncated normal distributions
- Model parameters included at the experimental level but not updated were distributed normally with truncation using the approach described in Marino et al. (2006).
- 3 chains thinned by 10 for 100K iterations; 1st 50K discarded

Table 1. Prior distributions for MCMC analysis of the CXR Database.

		M, Mean		S², Variance		Boundary Values	
Parameter	Label	Mean	CV	Shape	Scale	Lower	Upper
Maximum rate of resorption (µg/h/BW$^{0.75}$)	TMC	2900.0	2	3	0.446	54.4	30925
Affinity for resorption (µg/L)	KT	55	2	3	0.446	1.03	586.5
Fraction Unbound in plasma	Free	0.02	2	3	0.446	3.8x10^{-3}	0.213
		Lower	Upper				
Fraction of Kidney Blood Flow Filtered	FracFil	0.2	1	3	0.446	0.2	1

Results

Plasma

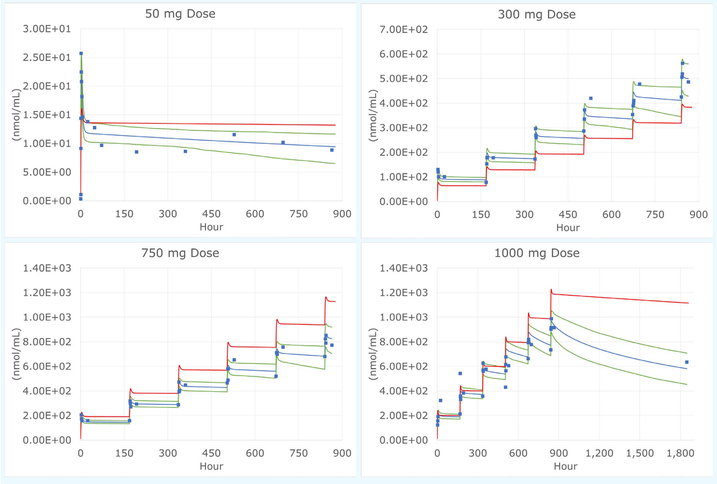


Figure 2. Simulation of measured PFOA plasma concentrations in 4 subjects using 500 iterations of the MCMC chains for each subject (Blue line = mean, Green lines = 95% CI, Red line = Loccisano model).

Urine

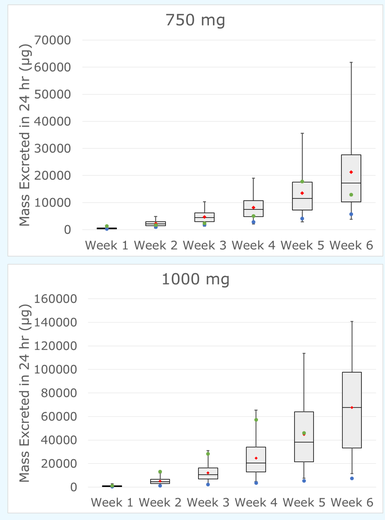


Figure 3. Simulation of measured mass of PFOA excreted in urine of 2 subjects using 500 iterations of the MCMC chains for each subject (Box = median and inter-quartiles, Error Bars = 95% CI, Red Diamond = mean, Green Dot = measured, Blue Dot = Loccisano model).

Results

Table 2. Posterior distributions for MCMC analysis of the CXR Database.

Parameter	Label	Mean (Mean; CV)	95% CI
Maximum rate of resorption (µg/h/BW$^{0.75}$)	TMC	3298; 0 078	1253; 6925
Affinity for resorption (µg/L)	KT	85.4; 0.12	50.1; 145.8
Fraction Unbound in plasma	Free	0.021; 0.14	0.010; 0.032
Fraction of Kidney Blood Flow Filtered	FracFil	0.237; 0.26	0.201; 0.340

- Scale reduction <1.2 for all parameters (Gelman diagnostic)
- Significant reduction in variance for all parameters
- TMC decreaed 30% from Locissano model
- Increase in affinity for resorption 85.4 from 55 µg/L with fraction unbound in plasma slightly increased (0.021)
- FracFil distribution indicates that resorption dominates clearance in human and the effective filtration rate is approximately equal to GFR

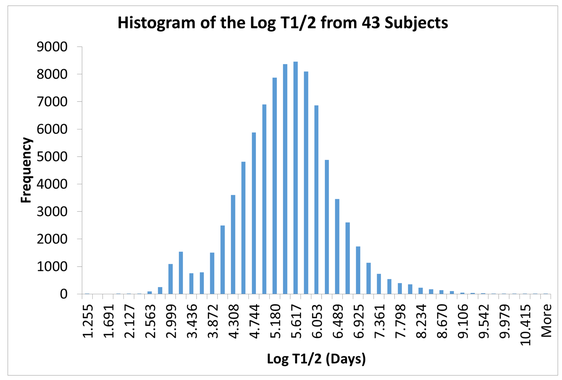


Figure 4. Histogram of the half-life distribution from the MCMC analysis of the CXR clinical study (0.1 mg dose bolus dose with half-life estimated at 2000 days; 2000 iterations of a posterior chain for each of the 43 subjects used to generate the frequency plot).

Conclusions

- Results from the calibration of the human PFOA model clearance parameters greatly improved the overall model fit to the CXR clinical database
- The CXR study data was highly informative for the human TMC and KT for resorption because plasma data were collected in both linear and non-linear regions of the dose-response.
- The availability of both plasma and urine data for the day of dosing was particularly valuable for estimating both the fraction unbound in plasma and the fractional kidney excretion
- The median half-life from the calibration was 0.6 years (95% CI: 0.1-4.2 years). This half-life for short-term clearance appears to be lower than the terminal half-lives derived from epidemiological studies, although based on confidence intervals the difference is not statistically significant.

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