

ORIGINAL ARTICLE

Application of a Physiologically Based Pharmacokinetic Model to Study Theophylline Metabolism and Its Interactions With Ciprofloxacin and Caffeine

A Navid*, DM Ng, SE Wong and FC Lightstone

Theophylline is a commonly used bronchodilator. However, due to its narrow therapeutic range, moderate elevation of serum concentration can result in adverse drug reactions (ADRs). ADRs occur because of interhuman pharmacokinetic variability and interactions with coprescribed medicines. We developed a physiologically based pharmacokinetic (PBPK) model of theophylline, caffeine, and ciprofloxacin metabolisms to: examine theophylline pharmacokinetic variability, and predict population-level outcomes of drug–drug interactions (DDIs). A simulation-based equation for personalized dosing of theophylline was derived. Simulations of DDI show that calculated personalized doses are safe even after cotreatment with large doses of strong inhibitors. Simulations of adult populations indicate that the elderly are most susceptible to ADRs stemming from theophylline–ciprofloxacin and theophylline–caffeine interactions. Females, especially Asians, due to their smaller average size, are more susceptible to DDI-induced ADRs following typical dosing practices. Our simulations also show that the higher adipose and lower muscle fractions in females significantly alter the pharmacokinetics of theophylline or ciprofloxacin.

CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 74–81; doi:10.1002/psp4.12061; published online 16 February 2016.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC? Inadvertent overdoses of theophylline occur because of interhuman pharmacokinetic variability and drug–drug interactions. Physicians use a dosing protocol to lower the possibility of adverse drug reactions. • WHAT QUESTION DOES THIS STUDY ADDRESS? How safe is the commonly used theophylline dosing practice for individuals of different populations? How dangerous are the drug–drug interactions of theophylline with caffeine and ciprofloxacin? What are the effects of sex and race differences on pharmacokinetics and pharmacodynamics of theophylline, caffeine, and ciprofloxacin? • WHAT THIS STUDY ADDS TO OUR KNOWLEDGE Simulation of drug–drug interactions show that commonly prescribed doses of theophylline are generally safe for male patients even when cotreated with relatively large doses of inhibitors. However, for women, because weight and body composition differences are not addressed, drug–drug interactions of theophylline with ciprofloxacin could be problematic. Because of their unique physique, Asian females are particularly at risk. • HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS It is important to account for size differences between sexes and races when prescribing theophylline. Use of personalized doses would reduce the chances of overdosing as well as harmful drug–drug interactions.

For nearly 80 years, theophylline (1,3 dimethylxanthine, THP) has been used as a bronchodilator for the treatment of obstructive airway diseases. While its relatively low efficacy and high frequency of side effects have resulted in lower use of THP in industrialized nations, the low cost of treatment makes it a preferred drug in the rest of the world.¹ Low-dose treatment with THP is generally safe and well tolerated.² THP also has the advantages that it can be administered orally, and can be used for treatment of steroid-resistant patients with severe asthma.³ Additionally, low-dose THP treatment has antiinflammatory and immunomodulatory benefits.^{4,5}

Despite these positive attributes, THP's narrow therapeutic range is problematic. Dose–response studies have shown that THP plasma concentrations ([THP]s) above 10 mg/L provide ample bronchodilation for treatment.¹ On the other hand, the threshold [THP] for initiation of ADRs is

20 mg/L.^{1,6} Thus, harmful [THP] can easily be reached through moderate overdoses.

The common features of severe theophylline toxicity are nausea, vomiting, diarrhea, gastrointestinal hemorrhage, hypokalemia, rhabdomyolysis, supraventricular and ventricular arrhythmias, sinus tachycardia, metabolic acidosis, and seizures.⁷ The incidences of toxicity are greater in the elderly and very young due to, respectively, diminished and premature activity of drug metabolizing enzymes.⁸

The large variability in human pharmacokinetics (PK) of THP makes it hard to use the same amount of the drug as a therapeutic dose for all patients. The dose required for reaching therapeutic concentration differs by fourfold among seemingly similar patients.⁹ In addition to individual differences in rates of drug clearance, DDIs can also significantly elevate average blood drug concentration. THP is primarily metabolized in the liver by the cytochrome P-450

isozyme 1A2 (CYP1A2).^{10,11} Concurrent use of drugs that are metabolized by CYP1A2 or inhibit its activity result in higher than anticipated [THP].

There are a large number of such drugs with varied therapeutic functions such as antibiotics (e.g., ciprofloxacin, CIP¹²), antidepressants, and even commonly used drugs like acetaminophen.¹³ CIP has a wide spectrum of antimicrobial activity and is used to treat many infections frequently seen in primary care, particularly those involving the respiratory and urologic systems.¹⁴

Caffeine (1,3,7-trimethylxanthine, CAF), the world's most popular drug, is demethylated by CYP1A2 to form THP along with other products.¹⁵ Thus, concurrent use of THP and CAF could have a significant effect on PK of THP.¹⁶ CAF not only competes with THP for CYP1A2 but also through its *in vivo* metabolism results in production of new THP (**Supporting Figure S1**). Given the prevalent usage of CAF and CIP, the possibility of concurrent use of these drugs with THP is high.

To gain a better understanding of THP absorption, distribution, metabolism, excretion, and toxicity (ADMET), we developed a whole-body physiologically based pharmacokinetic (PBPK) model of its metabolism. PBPK models are important tools for assessing toxicological risks.¹⁷ They provide a platform for integrating and interpreting data from disparate sources to predict the time-course of xenobiotic metabolisms. We used the model to study the magnitude of metabolic differences that could account for the variability of THP PK within a population. The model also simulates metabolism of CAF, paraxanthine (PX, the primary byproduct of CAF demethylation), and CIP. These features permit simulations of DDIs and provide a measure of transient changes in [THP] following coadministration with these drugs.

To date, a few other PBPK models of caffeine and theophylline have been developed^{10,18,19} and used to answer important pharmacological questions such as differences in ADMET of these compounds in neonates¹⁰ and pregnant women.¹⁸ However, none of these studies focused on DDIs of THP as well as a general population-wide analysis of its PK variability.

METHODS

The human body in the PBPK model is treated as 20 well-stirred homogenous compartments that are connected to one another via arterial and venous blood flow. The transient change in each compound's concentration in each organ is formulated mathematically as:

$$\frac{dC_i^\alpha(t)}{dt} = \frac{1}{V^\alpha} \left(Q^\alpha C_i^{ab}(t) - \frac{Q^\alpha C_i^\alpha(t)}{P_i^{\alpha:plasma}/BP} \right) + \frac{dY_i^\alpha(t)}{dt} - \frac{dZ_i^\alpha(t)}{dt} \quad (1)$$

where $C_i^\alpha(t)$ denotes the concentration of compound i in compartment α ; $C_i^{ab}(t)$ represents the concentration of compound i in the arterial blood; V^α is the volume of α ; Q^α is the blood flow into α and Y_i^α and Z_i^α are the amounts of i that are directly imported and removed from α , respectively. $P_i^{\alpha:plasma}$ and BP are respectively the tissue plasma

partition coefficient and blood to plasma ratio. In this model blood and stomach are the primary routes of introducing compounds into a system and hence might have a nonzero value for the term $\frac{dY_i^\alpha(t)}{dt}$. Introduction of a compound into a compartment with a single injection can be represented by the Dirac delta function such that:

$$\frac{dY_i^\alpha(t)}{dt} = D\delta(t) \quad (2)$$

where D denotes the dose. For single uptakes $\delta(t) = 1$ at $t = t_0$ and zero at all other times. For regular periodic uptakes: $\delta(t) = 1$ at $t = nT$, where n is an integer ($n = 0, 1, 2, \dots$) and T is the time interval between uptakes; $\delta(t) = 0$ at all other times.

For noneliminating tissues $\frac{dZ_i^\alpha(t)}{dt} = 0$. In the eliminating organs (liver and kidney), the value of $\frac{dZ_i^\alpha(t)}{dt}$ depends on the mode of elimination. For nonenzymatic or bulk elimination one can use:

$$\frac{dZ_i^\alpha(t)}{dt} = \frac{E_i^\alpha Q^\alpha C_i^{ab}(t)}{V^\alpha} \quad (3)$$

where a fraction of the drug ($E_i^\alpha < 1$) that is entering the tissue (compartment α) is extracted.²⁰ If a compound is metabolized, then information about the responsible enzymes and their affinity for compounds present in the system can be used to formulate $\frac{dZ_i^\alpha(t)}{dt}$ as:

$$\frac{dZ_i^\alpha}{dt} = \Delta_i^{met} \sum_{j=1}^n \frac{V_{\max,i,j} U_j^\alpha(t)}{K_{m,i,j} \left(1 + \sum_{l=1}^p \frac{U_l^\alpha(t)}{K_{i,l,j}} \right) + U_i^\alpha(t)} \quad (4)$$

where $U_j^\alpha(t)$ is the unbound concentration of the drug in compartment α (i.e., $U_j^\alpha(t) = C_j^\alpha(t) / P_j^{\alpha:plasma}/BP$), $K_{m,i,j}$ represents the Michaelis-Menten coefficient for interaction of compound i with enzyme j ; n denotes the number of enzymes in compartment α that can catalyze breakdown of drug i ; Δ_i^{met} is a coefficient that quantifies the difference in the hepatic metabolism of compound i for a patient (or a group) from that of average individuals; p designates the number of inhibitors that interact with j ; $U_l^\alpha(t)$ denotes the unbound concentration of inhibitor l in compartment α ; and $V_{\max,i,j}$ represents the maximum rate of metabolism of i by j . For cases when we do not have the inhibition constant ($K_{i,l,j}$), or the measured inhibition constant does not provide results that agree with experimental measurements, we assume that the enzyme-inhibitor complex is in equilibrium with the free enzyme and the inhibitor and we use K_m values instead of K_i . The ODEs that make up the model were solved by using the Mathematica suite of programs (v. 10.0, Wolfram Research, Champaign, IL). For additional details about the model see the **Supplementary Materials**.

RESULTS

Model validation

The model's predictions (henceforth predictions) were compared with experimental PK data. The predictions consistently

agree with measured dose-exposure data (henceforth measurements) in adults following uptake of different quantities of THP, CAF, and CIP (**Figure S2**). The calculated rates of drug clearance via hepatic and renal routes also agree with measurements. For THP, the predictions indicate that ~9–12% of the administered dose (125–500 mg) is excreted in the urine. This concurs with measurements (10–13% of the dose²¹).

For CIP, the predictions are that 78–92% of the administered dose (100–1000 mg) is excreted via urine. This agrees with measurements that show around 20% of the CIP is metabolized.²² **Figure S2c** shows that reduced renal clearance, a usual consequence of aging²³ can drastically affect the PK of CIP.

Predictions for peak plasma concentrations of the drugs (C_{max}), time to maximum concentration (T_{max}), and half-lives ($T_{1/2}$) also agree with measurements. For example, the measured $T_{1/2}$ of THP after uptake of a single 200 mg dose is 8.7 hours.²⁴ The predicted value is 9 hours. Another example, the average measured C_{max} following oral administration of 500 mg of CIP in healthy patients is 2.4 mg/L.²⁵ The predicted value is 2.45 mg/L.

Predictions of altered THP PK

The THP dose required for reaching therapeutic blood levels (10–20 mg/L) among the populace can range between 300–1600 mg/day.^{9,26} The predictions are that 8–11 mg/kg/day doses will affect therapeutic levels (**Figure S3**) in the commonly examined reference group (RG), i.e., healthy young patients in their 20s.

To gain a measure of alterations in average liver activities that could account for the large variability in THP dosing, the activities of the THP metabolizing enzymes were modified in the model to simulate different THP pharmacokinetics (see **Methods**). In male patients, the predictions indicate that for a dose of 300 mg/day to reach therapeutic levels and to avert an overdose after taking 1600 mg/day, the rate of THP metabolism has to be, respectively, 2.25 times lower and higher than the value for male RG. In women, the values are 1.75 times lower and 3 times faster than the value for female RG (**Figure S4**). The calculated maximum human adjustment kinetic factor for THP (HK_{AF}^{THP}) is 2.86.

Analysis of the common protocol for THP dosing in adults

Given the large variability in the PK of THP in a population, physicians use a common dosing initiation and titration protocol (DIT) to lower the possibility of ADRs. DIT (for adults (16–60 years) and children heavier than 45 kg) starts with a dose of 300 mg/day (divided Q6–8 hours). If the drug is tolerated for 3 days, the dose is increased to 400 mg/day. For elderly and patients with risk factors for impaired clearance, the dosage should not exceed this level. For others, after another 3 days, if tolerated, the dose is increased to 600 mg/day.⁹ The model was used to calculate the [THP] profile in adult patients when using DIT (**Figure 1**).

DIT distinguishes for age but not usually for sex.⁹ Given that women on average are 30% lighter than men,²⁷ if doses are not adjusted based on weight, the effective administered dose could be significantly higher than

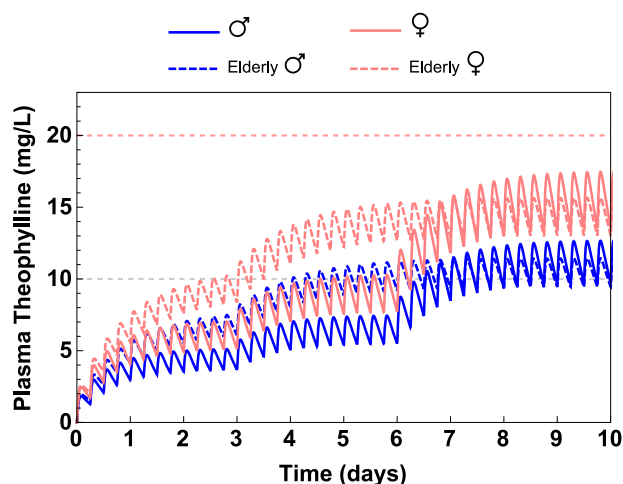


Figure 1 Simulated blood concentration of THP in patients using DIT based on their sex and age. Note that for the elderly the THP dose is not raised more than 400 mg/day while for the younger patients it is raised to 600 mg/day after 6 days. While DIT's age-based rules ensure that the average blood THP concentration in patients is similar regardless of age, by not differentiating based on sex (i.e., body habitus), the THP concentration drastically differs between the sexes. ♂ designates men and ♀ designates women. The dashed gray and red lines delineate the lower and upper edge of the therapeutic blood concentration range of THP.

intended. In addition, THP spreads poorly in body fat⁹ and women on average have a higher percentage of body fat and lower percentage of muscle than men.²⁷ Our simulations account for these differences and suggest that without adjusting THP therapy based on bodyweight, the odds of ADRs for women whose THP metabolism is moderately impaired drastically increases (**Figure 2**). To simulate changes in hepatic metabolism and renal clearance, we define Δ_{met} and Δ_{ren} as coefficients that quantify the differences in the metabolic activity and renal clearance of a patient from that of the RG (i.e.: $metabolism_{patient} = \Delta_{met} \times metabolism_{RG}$ and $renal\ clearance_{patient} = \Delta_{ren} \times renal\ clearance_{RG}$). Predictions show that while a 600 mg/day dose in young men with even significantly impaired metabolism ($\Delta_{met} \geq 0.65$) should not result in ADRs, young women need closer to normal THP metabolism ($\Delta_{met} \geq 0.85$) to avoid ADRs (**Figure 2**).

To simulate the PK of elderly patients, Δ_{met} and Δ_{ren} were reduced ($\Delta_{met} = 0.66$,²⁸ $\Delta_{ren} = 0.31$ ²⁹). Simulations show that the lower DIT doses taken by the elderly result in average [THP]s that are similar to those in RG (**Figure 1**). However, again because of size differences, the concentration is significantly higher in elderly women.

Derivation of an equation for predicting individualized THP doses

We simulated THP PK in patients with different Δ_{met} levels. Typically, a 5 mg/kg dose of THP achieves therapeutic levels for people with average THP metabolism. The simulations show that this dose would quickly affect plasma levels close to therapeutic levels even for small Δ_{met} levels (**Figure 3**). The results of simulations were used to derive a pair of

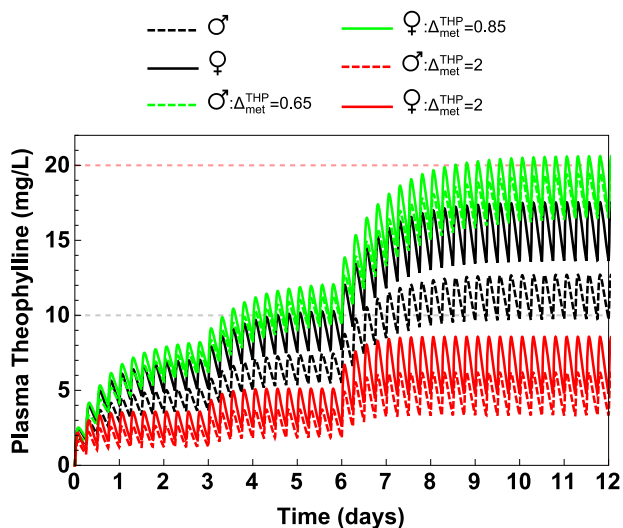


Figure 2 Model predicted plasma THP concentration profile following typical dose titration procedure used for adults. The recommended doses were divided and administered every 6 hours. ♂ designates young men and ♀ designates young women. Δ_{met}^{THP} values quantify THP metabolic level in comparison to average young persons. Values greater than 1 indicate faster metabolism while values smaller than 1 are indicative of slower THP metabolism.

hepatic metabolism activity (HMA) equations for men and women that calculate Δ_{met} . The HMA equations are:

$$\Delta_{met}^{male} = 10.3 - 0.97 \times C_{max}^* \quad (5)$$

$$\Delta_{met}^{female} = 10.5 - 0.91 \times C_{max}^* \quad (6)$$

where C_{max}^* is the measured maximum blood concentration of the patient (in mg/L) after a 5 mg/kg dose of THP.

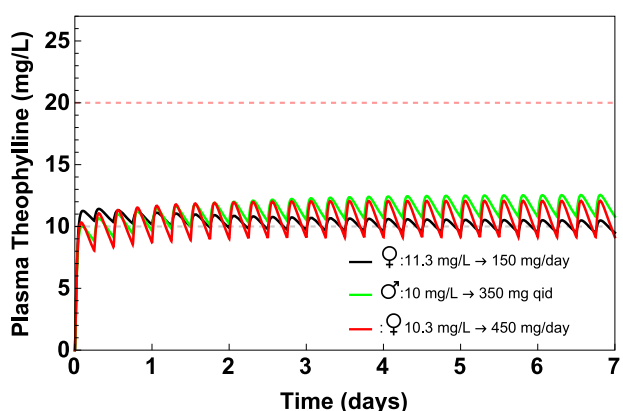


Figure 3 Model predicted plasma concentration profiles of three individuals with different C_{max}^* values. C_{max}^* is the measured maximum blood concentration of the patient taking a single 5 mg/kg dose of THP. The C_{max}^* values of 11.3, 10.3, and 10 result from 0.25, 1, and 2 times the normal hepatic metabolism of THP. The periodic THP doses used following initial THP uptake were determined using the PrD equation and were rounded to nearest multiple of 50. The doses predicted by PrD equation are safe even for highly altered metabolisms.

The HMA-calculated Δ_{met} on average differs from model predicted values by less than 7% (for $\Delta_{met} = 0.2-2.25$).

The predictions were used to derive another pair of equations for personalized dosing (PrD) based on the C_{max}^* value. The PrD equations are:

$$Dose_{male}^{mg/kg} = 82.2 - 7.7 \times C_{max}^* \quad (7)$$

$$Dose_{female}^{mg/kg} = 66.3 - 5.7 \times C_{max}^* \quad (8)$$

and provide a daily dose (in mg/kg) that should result in a THP blood level close to 10 mg/L (**Figure 3**). The values can be rounded to the nearest multiple of 50 without significant consequences. The equations are informative only if a clinician has the capability to measure a patient's C_{max}^* value. This might limit the use of the equations for informing treatment in developing countries.

Analysis of drug–drug interactions

Changes in PK of THP and CAF in RG following simultaneous administration of these drugs with various doses of CIP were simulated. The predictions were compared with measurements and are in good agreement (**Figures S5–S7**). There is a wide range of interindividual variability on the inhibitory effects of CIP on PK of THP and CAF.³⁰ This can be attributed to the interindividual variability in the amount liver CYP1A2.³⁰ In all cases the predictions are within the range of error for the measurements and close to the reported average values.

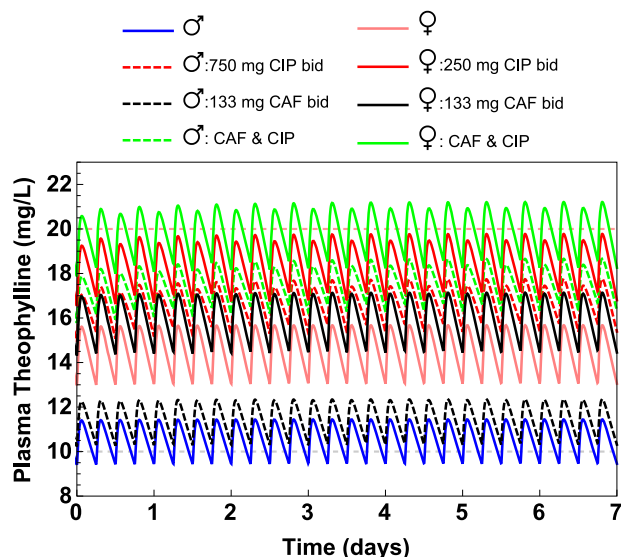


Figure 4 Model predicted outcome of DDI between THP-CAF, THP-CIP, and THP-CAF-CIP for average elderly patients taking 400 mg/day of THP. For men even coprescription with large doses of CIP and CAF should not result in ADRs. For women, as with their young counterparts, uptake of CIP more than minimal treatment dosage (500 mg/day) would result in ADRs. Consumption of CAF while taking THP and CIP would increase the odds of ADRs.

Table 1 Model predicted safe Δ_{met} values needed for different groupings of patients taking maximum DIT doses of THP (*600 mg/day for young and 400 mg/day for old patients)

Drug combination	Young men	Young women	Elderly men	Elderly women
THP*	0.62	0.87	0.35	0.51
THP & 266 mg CAF	0.67	0.93	0.39	0.55
THP & 960 mg CAF	0.79	<u>1.11</u>	0.48	<u>0.7</u>
THP & 500 mg CIP	0.7	0.99	0.45	0.65
THP & 1000 mg CIP	0.75	<u>1.05</u>	0.51	<u>0.75</u>
THP & 1500 mg CIP	0.82	<u>1.15</u>	0.58	<u>0.9</u>
THP & 266 mg CAF & 500 mg CIP	0.75	<u>1.05</u>	0.48	<u>0.7</u>
THP & 266 mg CAF & 1000 mg CIP	0.8	<u>1.12</u>	0.55	<u>0.8</u>
THP & 266 mg CAF & 1500 mg CIP	0.87	<u>1.22</u>	0.63	<u>0.92</u>
THP & 960 mg CAF & 500 mg CIP	0.86	<u>1.22</u>	0.56	<u>0.83</u>
THP & 960 mg CAF & 1000 mg CIP	0.92	<u>1.3</u>	0.64	<u>0.95</u>
THP & 960 mg CAF & 1500 mg CIP	0.98	<u>1.4</u>	<u>0.72</u>	<u>1.05</u>

Values that exceed the average Δ_{met} for a group, and will result in ADRs, are underlined. As can be seen, for women taking DIT doses of THP ($\Delta_{met}=1$ for young and 0.66 for elderly), taking any dose of CIP greater than 500 mg/day could result in ADRs. Consumption of caffeine increases the odds of ADRs.

Examination of theophylline drug–drug interactions

The model was used to examine PK of THP, CAF, and CIP DDIs (Figure 4, Table 1). At maximum DIT dose of 600 mg/day, RG men should be able to concurrently take large doses of CIP and CAF without any adverse outcomes (Table 1). At that dose, for RG women, anything more than small amounts of CIP (500 mg/day) could result in ADRs, and CAF uptake will increase the odds (Table 1).

Average elderly patients metabolize THP ($\Delta_{met} = 0.66$)²⁸ and clear CIP ($\Delta_{ren} = 0.31$)²⁹ at slower rates than RG. Predictions show average elderly men taking 400 mg/day of THP can take large doses of CIP and CAF without any ADRs (Figure 4, Table 1). For average elderly women taking 400 mg/day of THP, any treatment beyond minimal amounts of CIP (500 mg/day) could result in ADRs. CAF consumption will exacerbate the problem. Race-based differences in body habitus²⁷ can significantly affect PK of THP after DDI (Figure 5).

Evaluation of safety of PrD-calculated doses to drug–drug interactions

To assess the safety of PrD-calculated doses, THP PK were simulated in individuals with low levels of metabolism while they concurrently take THP along with large doses of CIP (1500 mg/day) and CAF (800 mg/day). Figure 6 shows that for individuals with normal renal function, the PrD-calculated dose is safe even for strong inhibitory DDI scenarios. However, for those with low Δ_{ren} (like the elderly), the calculated dose might lead to ADRs.

DISCUSSION

To alleviate frequent occurrence of THP-associated ADRs, we need a better understanding of its: (1) pharmacokinetics in different populations, (2) pharmacodynamics of common dosing practices, and (3) interactions with other commonly used drugs. Since PK of THP differs significantly among seemingly similar individuals,²¹ we developed a PBPB model to examine its interhuman PK variability and study

DDIs between THP and two other commonly used drugs, caffeine and ciprofloxacin.

Interhuman pharmacokinetic variability of theophylline

Typically, derivation of safe exposure levels of drugs in humans involves division of threshold levels for onset of ADRs from dose–response outcomes of animal experiments by a 100-fold uncertainty factor (human variability (10-fold) and interspecies differences (10-fold)). The human variability can be further subdivided into equal $10^{0.5}$ (=3.16) values for toxicodynamic and toxicokinetic differences.³¹

Unfortunately, the nonexistence of a measurable response in animal studies does not mean that: (i) there is not a human dose–response; or (ii) there is not a threshold for either therapeutic or adverse outcomes. Thus, we need to use the available biochemical and mechanistic data to develop computational models that can be used for human risk-assessment.

Since most of THP is metabolized within the liver,²¹ the variability in THP metabolism and DDI could stem from

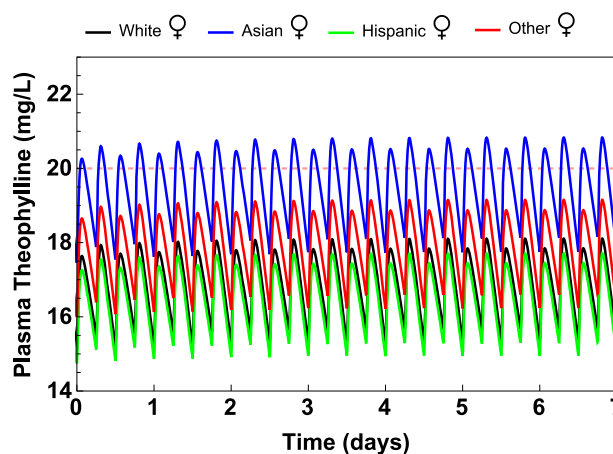


Figure 5 Prediction of PK in elderly women of different races taking 400 mg/day of THP and 500 mg/day of CIP. Asian females due to their unique body habitus are at a significantly higher risk for ADRs than their counterparts from other races.

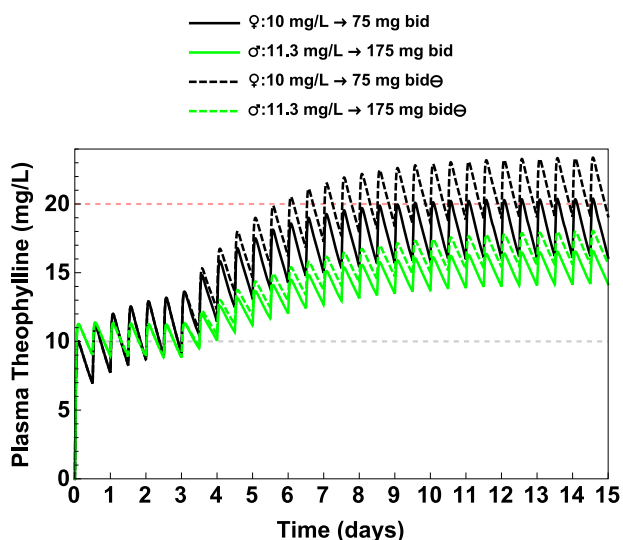


Figure 6 Model predicted plasma THP profile in four theoretical patients taking THP doses recommended by PrD equations and undergoing severe DDI (1500 mg/day of CIP and 800 mg/day of CAF (~6 cups of coffee)). The doses predicted using PrD equation do not result in ADRs for patients with severely impaired hepatic capabilities even when there is extreme metabolic inhibition due to DDI. However, patients with impaired hepatic and renal ($\Delta_{ren} = 0.31$, denoted by \ominus) capabilities (such as elderly), the equation predicted dose might result in ADRs.

wide-ranging interindividual differences in levels of CYP1A2 in liver microsomes.³⁰ The model predictions concur and show that even very low rates of renal clearance do not drastically affect THP pharmacokinetics (**Figure S2a**). Based on clinical data, the population-wide range of THP dosage is between 300 to 1600 mg/day.^{9,26} Using this information with our PBPK model, we calculated the HK_{AF}^{THP} to be 2.86.

Predicting individualized theophylline metabolism rates and safe dosage

Physicians use DIT as a means to avoid overprescribing THP.⁹ Although DIT accounts for the age of patients, it does not differentiate based on sex. Hence, females, who on average are 30% lighter than males,²⁷ receive a higher dose than men per unit weight. Studies have shown that for the same THP dose women have a much higher C_{max} , $T_{1/2}$, and AUC values than men. While some have reported slightly lower levels of CYP1A2 in females,³² generally after normalization by weight, measured PK differences are negligible.³³

Predictions show that neglecting sex-based size differences can have severe effects on pharmacodynamics of the drug. The model was used to examine pharmacokinetics of THP in RG (**Figure 1**) when using DIT. The results show that with DIT, [THP] in RG women reaches therapeutic levels (≥ 10 mg/L) significantly sooner than for young men and their average [THP] is ~40% higher than RG men. However, this higher level is below the ADR threshold and thus usually the dose is tolerated.

In young men, DIT is robust against significant levels of metabolic impairment (safe $\Delta_{met} = 0.62$) (**Figure 2, Table 1**). Thus, only for men with unusually slow metabolism (even

slower than average metabolism in elderly, $\Delta_{met} = 0.66$) the final dose needs to be adjusted to avoid ADRs. For young women (safe $\Delta_{met} = 0.87$), because of their higher average [THP], hepatic impairment greater than 10% from normal could lead to onset of ADRs (**Table 1, Figure 2**). For individuals with faster metabolism than RG, DIT will provide less therapeutic benefit since desired [THP] might not be reached (**Figure 2**).

Predictions show that when using DIT, the average [THP] is similar between young and old patients (**Figure 1**). But again due to differences in average weight between sexes, the average [THP] in women is significantly higher. The reduced DIT dose for the elderly is very effective at eliminating the possibility of ADRs, particularly in males (**Table 1, Figure 4**). Even in cases of extreme hepatic impairment, DIT treatment with THP alone is safe for average elderly patients (safe $\Delta_{met} = 0.35$ and 0.51 , respectively).

To optimize patient outcomes, predictions were used to derive two sex-based pairs of equations that use C_{max}^* to: (1) assess a patient's Δ_{met} (HMA equation), and (2) provide an individualized dose of THP (PrD equation). The C_{max}^* value generally can be measured about an hour after oral uptake of a dose of normal release formulation of THP. Theoretically, using PrD-calculated doses should eliminate the possibility of ADRs because the C_{max}^* value accounts for a patient's level of THP metabolism and adjusts the dosage accordingly. Simulations show that using PrD-calculated doses should quickly provide therapeutic doses needed for bronchodilation regardless of varying THP metabolic levels (**Figure 3**).

The predictions of the PrD and HMA equations have not been used in a clinical setting. To test the utility and safety of predicted values, a study should be set up where clinicians measure the average [THP] in a diverse population of low-risk volunteers who are treated with formula-predicted doses. If the results are proven to be reliable and safe, then the application could be expanded to the general populace.

Examination of drug–drug interactions between theophylline, caffeine, and ciprofloxacin

DDIs can appreciably raise the average levels of drugs in the body. For THP, this is because CYP1A2, the primary THP metabolizing enzyme, interacts with a large number of other drugs. This reduces the effective concentration of enzymes for metabolizing THP. Caffeine is one such drug and is usually consumed without consideration for its DDIs, although it significantly affects the PK of many drugs.¹³ Another drug that exhibits DDI with THP is ciprofloxacin, a commonly used broad-spectrum antibiotic.

To gain a quantitative understanding of the PK effects of these DDIs, the model was used to simulate simultaneous uptake of different combinations of these drugs. The primary outcomes of DDIs are decreased clearance of the drugs from the system (i.e., increased AUC , $T_{1/2}$, and C_{max}) (**Figures S5–S7**).

Theophylline–caffeine interaction. DDI-induced alterations in the PK of drugs can result in serious pharmacodynamic outcomes. For example, CAF, like THP, is a bronchodilator

and stimulates the central nervous system, as well as diuresis and lipolysis.³⁴ Simultaneous uptake of CAF and THP could amplify these physiological effects.

Even alone, high CAF levels can be toxic. ADRs for CAF are observed at plasma concentrations exceeding 40 mg/L³⁴ and concentrations above 80 mg/L are considered lethal.³⁵ The average daily adult CAF consumption is ~300 mg³⁵ and predictions indicate that this level of consumption should not result in ADRs in the majority of the population (**Figure S2b**).

For a 600 mg/day of THP (i.e., highest DIT dose), predictions show that even heavy consumption of CAF (960 mg/day, similar to 12 espresso shots) should not result in ADRs in men (**Table 1**). However, this extreme level of CAF consumption can result in ADRs in female patients (**Table 1**).

Theophylline–ciprofloxacin interaction. The dosing of CIP alone for a variety of different types of infections were simulated (**Figure S8**), and the average CIP concentrations (0.4–2.1 mg/L) are within the range of measured CIP MIC₉₀ values for a majority of pathogenic bacteria (0.008–2 g/L³⁶). Only some strains of *streptococci* and *staphylococci* require more rigorous treatments.^{37,38}

Even alone, there are a number of ADRs associated with excess CIP exposure including gastrointestinal or neurological symptoms.^{39,40} Simulations show that CIP DDIs with CAF and THP do not significantly alter the plasma concentration of CIP (results not shown). This would be expected since the majority of CIP is cleared through the kidneys.

PK analyses of CIP have shown that if weight differences are accounted for, there is no difference in PK of CIP between the sexes.⁴¹ Studies have also shown that CIP clearance is significantly slower in elderly patients.⁴¹ This has been attributed to diminished renal clearance capacity in these patients.²⁹

DDI with CIP can significantly effect the plasma concentration of methylxanthines (**Figures S5–S7**).^{12,30,42,43} Predictions show that DDI with even large doses of CIP should not result in ADRs for men taking 600 mg/day of THP (**Table 1, Figure 4**). However, even for men, simultaneous treatment with large doses of THP, CIP, and CAF necessitates almost perfect hepatic metabolism capacity to avoid ADRs (**Table 1**).

For women, predictions indicate that when taking a maximum DIT dose of THP, any treatment with CIP greater than 500 mg/day (minimal dose used for treatment of minor infections like uncomplicated urinary tract infections) could result in ADRs. Under these circumstances, even normal consumption of CAF can increase the odds of ADRs.

As noted, this significant PK difference between sexes is due to overlooking size differences between men and women. Some have suggested that differences in adipose and muscle content between men and women might be a factor for the PK differences. Our results support this hypothesis. We instituted sex-based body habitus differences in our model and the PK differences were significant (7% higher AUC in women, (**Figure S9**)) when weight differences were normalized).

We analyzed the differences between women of diverse races and based on differences in average body mass our simulations indicate that Asian women are significantly more likely to encounter ADRs from THP treatment than other females. For example, while simulations show that concurrent treatment with 400 mg/day of THP and 500 mg/day of CIP should not lead to ADRs in most elderly female patients, elderly Asian women are susceptible (**Figure 5**).

Finally, we decided to test the safety of doses predicted by the PrD equation to various levels of DDI. **Figure 6** shows that for individuals with low levels of THP metabolism, the predicted doses are resistant to DDIs. But in cases where the patient has diminished renal clearance (e.g., elderly), extreme DDI with CIP could lead to onset of ADRs. This is because the PrD-calculated dose is based on a patient's THP metabolism levels reflected in C_{max}^* , but low renal clearance strongly elevates levels of CIP in the body (**Figure S2c**) and exacerbates inhibition of THP metabolism.

Acknowledgments. The work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344. The project (12-SI-004) was funded by the Laboratory Directed Research and Development program at LLNL. This material is based upon work supported by the S.D. Bechtel, Jr. Foundation, National Marine Sanctuary Foundation, Carnegie Corporation of New York, and/or National Science Foundation under Grant Nos. 0952013 and 0833353. Any opinions, findings, and conclusions, or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the funders. The authors thank Dr. Gary Ginsberg and Dr. Mike Malfatti for their helpful correspondence. LLNL-JRNL-668940.

Conflict of Interest. The authors declare that they have no competing interests.

Author Contributions. A.N. and F.C.L. wrote the article; A.N. designed the research; A.N. and D.M.N. performed the research; A.N., D.M.N., and S.E.W. analyzed the data.

1. Barnes, P.J. Theophylline in chronic obstructive pulmonary disease: new horizons. *Proc. Am. Thorac. Soc.* 2, 334–339 (2005).
2. Zhou, Y. et al. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. *Respirology* 11, 603–610 (2006).
3. Boswell-Smith, V., Cazzola, M., & Page, C.P. Are phosphodiesterase 4 inhibitors just more theophylline? *J. Allergy Clin. Immunol.* 117, 1237–1243 (2006).
4. Sullivan, P., Jaffar, Z., Page, C., Costello, J., Bekir, S. & Jeffery, P. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. *Lancet* 343, 1006–1068 (1994).
5. Ward, A.J.M., McKenniff, M., Evans, J.M., Page, C.P. & Costello, J.F. Theophylline—an immunomodulatory role in asthma? *Am. Rev. Respir. Dis.* 147, 518–523 (1993).
6. Rall, T.W. Central nervous system stimulants: the xanthines. In: *The Pharmacological Basis of Therapeutics*, Vol. 6 (eds. Goodman, A.G., Gilman, L.S., and Goodman, A.) 592–607 (Macmillan, New York, 1980).
7. Vale, A. Theophylline. *Medicine* 35, 657 (2007).
8. Hurwitz, N. Predisposing factors in adverse reactions to drugs. *Br. Med. J.* 1, 536 (1969).
9. Sandow, N. *RxList: The Internet Drug Index*. <<http://www.rxlist.com>> (1995).
10. Ginsberg, G., Hattis, D., Russ, A. & Sonawane, B. Physiologically based pharmacokinetic (PBPK) modeling of caffeine and theophylline in neonates and adults: implications for assessing children's risks from environmental agents. *J. Toxicol. Environ. Health, Part A* 67, 297–329 (2004).

11. Sarkar, M.A., Hunt, C., Guzelian, P.S. & Karnes, H.T. Characterization of human liver cytochromes P-450 involved in theophylline metabolism. *Drug Metab. Dispos.* **20**, 31–37 (1992).
12. Raouf, S., Wollschlaeger, C. & Khan, F.A. Ciprofloxacin increases serum levels of theophylline. *Am J. Med.* **82**, 115–118 (1987).
13. Carrillo, J.A. & Benitez, J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin. Pharmacokinet.* **39**, 127–153 (2000).
14. LeBel, M. Ciprofloxacin: chemistry, mechanism of action, resistance, antimicrobial spectrum, pharmacokinetics, clinical trials, and adverse reactions. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **8**, 3–30 (1988).
15. Tassaneeyakul, W. *et al.* Caffeine metabolism by human hepatic cytochromes P450: contributions of 1A2, 2E1 and 3A isoforms. *Biochem. Pharmacol.* **47**, 1767–1776 (1994).
16. Robson, R.A. *et al.* Characterisation of theophylline metabolism by human liver microsomes: inhibition and immunochemical studies. *Biochem. Pharmacol.* **37**, 1651–1659 (1988).
17. Clark, L.H., Setzer, R.W. & Barton, H.A. Framework for evaluation of physiologically-based pharmacokinetic models for use in safety or risk assessment. *Risk Anal.* **24**, 1697–1717 (2004).
18. Gaohua, L., Abduljalil, K., Jamei, M., Johnson, T.N. & Rostami-Hodjegan, A. A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4. *Br. J. Clin. Pharmacol.* **74**, 873–885 (2012).
19. Shi, J., Benowitz, N.L., Denaro, C.P. & Sheiner, L.B. Pharmacokinetic-pharmacodynamic modeling of caffeine: tolerance to pressor effects. *Clin. Pharmacol. Ther.* **53**, 6–14 (1993).
20. Poulin, P. & Theil, F.P. Prediction of pharmacokinetics prior to in vivo studies. II. Generic physiologically based pharmacokinetic models of drug disposition. *J. Pharm. Sci.* **91**, 1358–1370 (2002).
21. Upton, R.A. *et al.* Intraindividual variability in theophylline pharmacokinetics: statistical verification in 39 of 60 healthy young adults. *J. Pharmacokinet. Biopharm.* **10**, 123–134 (1982).
22. Rohwedder, R.W., Bergan, T., Thorsteinsson, S.B. & Scholl, H. Transintestinal elimination of ciprofloxacin. *Diagn. Microbiol. Infect. Dis.* **13**, 127–133 (1990).
23. Vlassara, H., Ferrucci, L., Post, J. & Striker, G. Decline of renal function in normal aging, role of oxidants/inflammation: when does it begin: is it inevitable, preventable, or treatable? In: *Geriatric Nephrology Curriculum* (eds Oreopoulos, D.G. and Wiggins, J.) 1–9 (American Society of Nephrology, 2009).
24. Antal, E.J., Kramer, P.A., Mercik, S.A., Chapron, D.J. & Lawson, I.R. Theophylline pharmacokinetics in advanced age. *Br. J. Clin. Pharmacol.* **12**, 637–645 (1981).
25. Crump, B.R., Wise, R. & Dent, J. Pharmacokinetics and tissue penetration of ciprofloxacin. *Antimicrob. Agents Chemother.* **24**, 784–786 (1983).
26. Burki, N.K. The effects of the combination of inhaled ipratropium and oral theophylline in asthma. *CHEST J.* **111**, 1509–1513 (1997).
27. Carpenter, C.L. *et al.* Body fat and body-mass index among a multiethnic sample of college-age men and women. *J. Obes.* **2013** (2013).
28. Li, Z. & Chen, G. Evaluation of theophylline population pharmacokinetics in adult hospitalized patients using NONMEM analysis. *Acta Pharmacol. Sinica* **15**, 267–270 (1994).
29. LeBel, M., Barbeau, G., Bergeron, M.G., Roy, D. & Vallee, F. Pharmacokinetics of ciprofloxacin in elderly subjects. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **6**, 87–91 (1986).
30. Batty, K.T., Davis, T.M., Ilett, K.F., Dusci, L.J. & Langton, S.R. The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects. *Br. J. Clin. Pharmacol.* **39**, 305–311 (1995).
31. WHO. Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. In: *Environmental Health Criteria*, Vol. 170 (ed. Organization, W.H.) (Geneva, Switzerland, 1994).
32. Relling, M.V., Lin, J.S., Ayers, G.D. & Evans, W.E. Racial and gender differences in N-acetyltransferase, xanthine oxidase, and CYP1A2* activities. *Clin. Pharmacol. Ther.* **52**, 643–658 (1992).
33. Jusko, W.J., Gardner, M.J., Mangione, A., Schentag, J.J., Koup, J.R. & Vance, J.W. Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. *J. Pharm. Sci.* **68**, 1358–1366 (1979).
34. Fredholm, B.B. On the mechanism of action of theophylline and caffeine. *Acta Med. Scand.* **217**, 149–153 (1985).
35. Banerjee, P., Ali, Z., Levine, B. & Fowler, D.R. Fatal caffeine intoxication: a series of eight cases from 1999 to 2009. *J. Forensic Sci.* **59**, 865–868 (2014).
36. Tartaglione, T.A., Raffalovich, A.C., Poyner, W.J., Espinel-Ingroff, A. & Kerkering, T.M. Pharmacokinetics and tolerance of ciprofloxacin after sequential increasing oral doses. *Antimicrob. Agents Chemother.* **29**, 62–66 (1986).
37. Chin, N.-X. & Neu, H.C. Ciprofloxacin, a quinolone carboxylic acid compound active against aerobic and anaerobic bacteria. *Antimicrob. Agents Chemother.* **25**, 319–326 (1984).
38. Eliopoulos, G.M., Gardella, A. & Moellering, R.C. In vitro activity of ciprofloxacin, a new carboxyquinolone antimicrobial agent. *Antimicrob. Agents Chemother.* **25**, 331–335 (1984).
39. Schacht, P., Arcieri, G. & Hullmann, R. Safety of oral ciprofloxacin: an update based on clinical trial results. *Am. J. Med.* **87**, S98–S102 (1989).
40. Shepard, C.W. *et al.* Antimicrobial postexposure prophylaxis for anthrax: adverse events and adherence. *Emerging Infect. Dis.* **8**, 1124–1132 (2002).
41. Shah, A., Lettieri, J., Nix, D., Wilton, J. & Heller, A.H. Pharmacokinetics of high-dose intravenous ciprofloxacin in young and elderly and in male and female subjects. *Antimicrob. Agents Chemother.* **39**, 1003–1036 (1995).
42. Mahr, G. *et al.* Effects of temafloxacin and ciprofloxacin on the pharmacokinetics of caffeine. *Clin. Pharmacokinet.* **22**, 90–97 (1992).
43. Harder, S., Staib, A.H., Beer, C., Papenburg, A., Stille, W. & Shah, P.M. 4-Quinolones inhibit biotransformation of caffeine. *Eur. J. Clin. Pharmacol.* **35**, 651–656 (1988).

© 2016 The Authors CPT: Pharmacometrics & Systems Pharmacology published by Wiley Periodicals, Inc. on behalf of American Society for Clinical Pharmacology and Therapeutics. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (<http://www.wileyonlinelibrary.com/psp4>)