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ARTICLE

Prediction of cytochromes P450 3A and 2C19 modulation by both inflammation and drug interactions using physiologically based pharmacokinetics

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Abstract

Xenobiotics can interact with cytochromes P450 (CYPs), resulting in drug–drug interactions, but CYPs can also contribute to drug–disease interactions, especially in the case of inflammation, which downregulates CYP activities through pretranscriptional and posttranscriptional mechanisms. Interleukin-6 (IL-6), a key proinflammatory cytokine, is mainly responsible for this effect. The aim of our study was to develop a physiologically based pharmacokinetic (PBPK) model to foresee the impact of elevated IL-6 levels in combination with drug interactions with esomeprazole on CYP3A and CYP2C19. Data from a cohort of elective hip surgery patients whose CYP3A and CYP2C19 activities were measured before and after surgery were used to validate the accurate prediction of the developed models. Successive steps were to fit models for IL-6, esomeprazole, and omeprazole and its metabolite from the literature and to validate them. The models for midazolam and its metabolite were obtained from the literature. When appropriate, a correction factor was applied to convert drug concentrations from whole blood to plasma. Mean ratios between simulated and observed areas under the curve for omeprazole/5-hydroxy omeprazole, esomeprazole, and IL-6 were 1.53, 1.06, and 0.69, respectively, indicating an accurate prediction of the developed models. The impact of IL-6 and esomeprazole on the exposure to CYP3A and CYP2C19 probe substrates and respective metabolites were correctly predicted. Indeed, the ratio between predicted and observed mean concentrations were <2 for all observations (ranging from 0.51 to 1.7). The impact of IL-6 and esomeprazole on CYP3A and CYP2C19 activities after a hip surgery were correctly predicted with the developed PBPK models.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

There is high interindividual variability in cytochrome P450 (CYP) activities due to genetic, environmental, and physiological factors, including drug–drug and

drug–disease interactions. The development and use of a physiologically based pharmacokinetic (PBPK) model allow for the prediction of the pharmacokinetic properties of a drug and have been used to predict and assess drug efficacy and safety.

WHAT QUESTION DID THIS STUDY ADDRESS?

Did the PBPK models developed accurately predict the impact of elevated interleukin-6 (IL-6; acute inflammation) in combination with drug interactions with esomeprazole on CYP3A and CYP2C19 activities?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The impact of IL-6 and esomeprazole on exposure to the CYP3A and CYP2C19 probe substrates and their respective metabolites were correctly predicted by the developed PBPK models.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The integration and prediction of pharmacodynamic and disease parameters in PBPK models appear to be a promising approach to personalize treatments.

INTRODUCTION

The interplay of genetic, physiological, and environmental factors leads to interindividual and intraindividual variability in response to treatment.[1] Indeed, these factors are unique to each individual and/or may change over time and cause disparity in the safety and efficacy of treatments.[1] Precision medicine is a leading approach in the transformation of medicine, aiming to tailor treatments according to the biological and genetic characteristics of individuals.[2] By using the "five rights of medication administration," personalized medicine supports optimization of therapy in terms of efficacy and safety and thus public health and healthcare costs.[3] In fact, one size does not fit all, and 40%–70% of patients have a lack of efficacy or safety in their pharmacological therapy.[4]

The causes of variability in drug responses and the interaction between the body and the drug must be better considered to personalize medicine.[5] Cytochromes P450 (CYPs) are the major enzymes involved in drug metabolism and responsible for about three-quarters of drugs cleared by metabolism.[6] It is estimated that 15%–30% of the variability in their activities is caused by genetic polymorphisms, but other nongenetic factors may also greatly contribute to this observed variability.[4,7] Xenobiotics and endogenous substances may inhibit or induce CYP activity such as the well-known modulation of CYP activities by certain concomitant treatments, resulting in pharmacokinetic (PK) drug–drug interactions (DDIs).[8] In vitro and animal model data as well as smaller human data support the theory that inflammation downregulates CYP activities, resulting in a PK drug–disease interaction.[9]

Inflammation is a complex biological protective response to stimuli such as pathogens, damaged cells, or irritants.[10] It involves a large repertoire of host cells, blood vessels, proteins, and numerous mediators to eliminate the initial cause and launch the healing process.[10] Immune cells are activated by the pattern-recognition receptors to trigger the inflammatory response and are considered to be the main source of various proinflammatory mediators, such as cytokines.[10] Main proinflammatory cytokines are interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, and they are deemed as the most important mediators of acute phase protein synthesis in hepatocytes.[10,11] IL-6 is a critical cytokine that mediates many inflammatory and immunomodulatory pathways against a multitude of environmental and infectious stimuli.[12] IL-6 levels increase to a maximum between 4 and 48 h after surgery and drop rapidly after 48 to 72 h.[13]

The mechanism of modulation of CYP activities by inflammation is complex and includes a wide variety of ligand-activated transcription factors and mediators, but the cytokine-mediated alteration of gene transcription is the major mechanism of modulation.[7] The downregulation of CYP during the inflammatory response can occur through transcriptional downregulation of transcription factors, interference with dimerization/translocation of transcription factors, alteration of liver-enriched CCAATT/enhancer-binding protein signaling, or direct regulation by nuclear factor-κB or posttranscriptional mechanisms via microRNAs.[7] The principal mechanisms are through the transcription factors pregnane X receptor (PXR) and constitutive androstane receptor (CAR), leading to variation in the sensitivity of different CYPs to inflammation.[7] Indeed, CYP3A, CYP2C9, and CYP2C19

are regulated by PXR and CAR and are more sensitive to inflammation, whereas the aryl hydrocarbon receptor regulated CYP1A2 isoform is less sensitive.[7] CYP2D6 is the least affected CYP because it is not inducible by nuclear receptors and seems therefore not affected by inflammation-induced alterations.[7]

Personalized medicine aims to enable the design of a virtual representation of the patient and the development of predictive models based on known interactions between molecular, environmental, and lifestyle data by a computational algorithm as a decision support to individualize treatment.[2]

Dynamic physiologically based PK (PBPK) models are used to predict plasma concentration curves by simulating the concentration-time profiles of a drug and its metabolite(s) in plasma or in an organ of interest and simultaneously allow estimation of PK parameters.[14] The PBPK approach has been included in regulatory guidance and the development of new drugs and new drug applications.[14] The understanding of some of the causes of absorption, distribution, metabolism, and excretion (ADME) changes that occur in different disease states has improved, and consequently PBPK modeling has been used to simulate drug disposition in special populations.[14] In fact, PBPK models combined with in vitro–in vivo extrapolation allow the description of many phenomena involved in complex PK processes, integrating prior knowledge of the anatomical, physiological, and biochemical characteristics of the body as well as the physicochemical properties of the drug.[15] Therefore, the lack of in vivo data in patient populations contribute to limiting the application of PBPK modeling to predict PK in disease populations.[14]

The aim of our study was to develop a PBPK model that simultaneously characterizes the impact of IL-6 and CYP2C19 inhibition by esomeprazole on the PK of midazolam and omeprazole, two probe substrates used to assess the activities of CYP3A (CYP3A4 and CYP3A5) and CYP2C19 in patients undergoing elective hip surgery.[16] We aimed to quantitatively predict the clinical drug-drug-disease interaction on CYP3A and CYP2C19 activities.

METHODS

PK data

PK data were obtained from the raw data of our recently published cohort study, which assessed the activity of the six major CYP isoforms (cocktail approach) before and after elective hip surgery.[16] A total of 30 patients received the "Geneva cocktail" before and 1 and 3 days after surgery and at discharge (5 to 6 days after surgery).[16] The composition of this oral cocktail and the sampling and analytical methods to assess the concentration of probe substrates and their metabolites have been described previously.[16] The study population did not take CYP inhibitors or inducers, with the exception of esomeprazole in the postoperative setting, as this is a routine prescription after surgery in the hospital where the cohort study was conducted.[16]

Systemic IL-6 concentrations in surgical patients

Systemic levels of IL-6 were also systematically measured before surgery, the first 3 days after surgery, and at discharge.[16] Sample preparation and analytical methods for IL-6 determination have been described elsewhere.[16] The population mean and standard deviation (SD) of systemic levels of IL-6 were calculated for each day.

PBPK models

PBPK models of midazolam (CYP3A) and omeprazole (CYP2C19) in virtual surgical patients were developed using the ADME simulator Simcyp™ Version 19 (Certara®, Simcyp Limited). The virtual population with surgery-related inflammation was characterized by incorporating the impact of systemic IL-6 (inhibitor 1) level and esomeprazole (inhibitor 2) intake on hepatic and intestinal expressions of CYP3A and CYP2C19 of the default healthy Caucasian population. General aspects of PBPK model characteristics, enzyme dynamics, and victim drug kinetics in the ADME simulator have been described previously.[17,18] As a first step, the simulator built-in library models of midazolam and omeprazole were used in the current PBPK models to characterize the plasma concentrations of these CYP3A and CYP2C19 substrates. However, the default simulated concentration-time profile of omeprazole did not match the concentration-time profile of omeprazole in a population of Caucasian healthy volunteers (data not shown).[19] Based on a previously validated model, volume of distribution at steady state (Vss) of omeprazole was changed from 0.15 to 0.23 L/kg because the default value did not fit the Caucasian population.[20,21] The models used for midazolam and omeprazole are summarized in Table S1 and Table 1, respectively.

Modeling of midazolam metabolite

The metabolism of midazolam is almost exclusively performed by CYP3A to 1-hydroxymidazolam (1-OH-MDZ). Indeed, 1-OH-MDZ, 4-OH-MDZ, and 1,4-OH-MDZ

TABLE 1 Parameters for omeprazole and 5-OH-OMPZ

Parameters	Omeprazole	5-OH-OMPZ[25]
Molecular weight (g/mol)	345.4	361.4
logP	2.33	1.1
Compound type	Ampholyte	Ampholyte
pKa	9.33; 4.31	9.29; 3.93
B/P	0.59	0.59 (assumed)
fu,p	0.053	0.17
Absorption		
Model	First order	NA
Fraction absorbed	Predicted	NA
fu,gut	0.053	NA
Extrapolated Peff, man (10^{-4} cm/s)	12	NA
MDCK II (10^{-6} cm/s)	59	NA
Distribution		
Model	Minimal PBPK	Minimal PBPK
Vss (L/kg)	0.23[21]	0.1 (adjusted parameter)
Elimination		
Enzyme kinetics		
Cl_{int} CYP2C19 in recombinant (µl/min/pmol of isoform)	62.593	NA
fumic CYP2C19	1	NA
Cl_{int} CYP3A4 in recombinant (µl/min/pmol of isoform)	0.201	NA
fumic CYP3A4	1	NA
Cl_R (L/h)	0	0
Additional systemic clearance (L/h)	NA	45 (adjusted parameter)
$Kapp_{CYP2C19}$ (µM)	0.65	NA
$kinact_{CYP2C19}$ (h^{-1})	2.9	NA

Abbreviations: B/P, blood-to-plasma partition ratio; Cl_{int}, in vitro intrinsic clearance; Cl_R, renal clearance; CYP, cytochrome P450; fu,gut, unbound fraction of drug in enterocytes; fumic, fraction of unbound drug in the in vitro microsomal incubation; fu,p, fraction unbound in plasma; Kapp, concentration of mechanism-based inhibitor associated with half maximal inactivation rate; kinact, inactivation rate of the enzyme; MDCK II, Madin-Darby canine kidney permeability cell line; NA, not applicable; PBPK, physiologically based pharmacokinetic; Peff,man, human jejunum effective permeability; pKa, acid dissociation constant at logarithmic scale; Vss, volume of distribution at steady state; 5-OH-OMPZ, 5-hydroxy-omeprazole.

account for 75%, 3%, and <1% of the metabolites, respectively.[22] In this PBPK model, a previously described and validated model for 1-OH-MDZ was used (Table S1).[23]

Modeling of omeprazole metabolite

Omeprazole is almost exclusively metabolized by CYP2C19 in 5-hydroxyomeprazole (5-OH-OMPZ), as 60.5%, 25%, and 14.5% of the racemate is metabolized to 5-OH-OMPZ, 5-O-desmethyl-OMPZ, and OMPZ-sulfone, respectively.[24] We used a previously published and validated model as the basis for implementing this metabolite in our PBPK model.[25] However, the renal clearance (Cl_R) was changed from 0.037 to 0 L/h to be consistent with that of the built-in library model of omeprazole (Table 1).

Modeling of esomeprazole

A previously developed and validated PBPK model was used for esomeprazole, the S-isomer of omeprazole (Table 2).[25] This published model considered that

TABLE 2 Parameters for esomeprazole

Parameters	Esomeprazole as published [25]	Esomeprazole as used
Molecular weight (g/mol)	345.4	345.4
logP	2.23	2.23
Compound type	Ampholyte	Ampholyte
pKa	4.4; 8.7	4.4; 8.7
B/P	0.59	0.59
fu,p	0.03	0.03
Absorption		
Model	First order	First order
fa	1	1
ka (/h)	2	2
Lag time (h)	0	0
MDCK II Perm (10^{-6} cm/s)	59	59
Extrapolated Peff, man (10^{-4} cm/s)	12	12
Distribution		
Model	Minimal PBPK	Minimal PBPK
Vss (L/kg)	0.2	0.2
Elimination		
Cl_R (L/h)	0.037	0
Enzymes kinetics		
$Cl_{intCYP2C19}$ (µl/min/pmol of isoform)	24.3	24.3
$Ki_{CYP2C19}$ (µM)	8.4	8.4
$Kapp_{CYP2C19}$ (µM)	0.2706	0.2706
$kinact_{CYP2C19}$ (/h)	1.74	1.74
$fumic_{CYP2C19}$	1	1
$Cl_{intCYP3A4}$ (µl/min/pmol of isoform)	0.36	0.36
Ki_{CYP3A4} (µM)	40	40
$Kapp_{CYP3A4}$ (µM)	1.716	NA
$kinact_{CYP3A4}$ (/h)	1.74	NA
$fumic_{CYP3A4}$	1	1

Abbreviations: B/P, blood-to-plasma partition ratio; Cl_{int}, in vitro intrinsic clearance; Cl_R, renal clearance; CYP, cytochrome P450; fa, fraction absorbed; fu,gut, unbound fraction of drug in enterocytes; fumic, fraction of unbound drug in the in vitro microsomal incubation; fu,p, fraction unbound in plasma; ka, first-order absorption rate constant; Kapp, concentration of mechanism-based inhibitor associated with half maximal inactivation rate; Ki, concentration of inhibitor that supports half maximal inhibition; kinact, inactivation rate of the enzyme; MDCK II Perm, Madin-Darby canine kidney permeability cell line; NA, not applicable; Peff,man, human jejunum effective permeability; pKa, acid dissociation constant at logarithmic scale; Vss, volume of distribution at steady state.

esomeprazole was both a reversible and irreversible inhibitor of CYP2C19 and CYP3A4, even though its effect on CYP3A4 is not usually considered relevant in clinical practice.[8,26,27] Published data indeed suggest a short-term effect of esomeprazole on midazolam concentration but no irreversible CYP3A inhibition, even with twice the dose used for the current simulation.[28,29] The irreversible inhibition of CYP3A4 by esomeprazole (mechanism-based inhibition) was thus removed from the simulation. However, both inhibitions of CYP2C19 were kept in the model because it is accepted in the literature that esomeprazole is a CYP2C19 reversible and irreversible inhibitor.[28,29] Moreover, the Cl_R was changed from 0.037 to 0 L/h, as well as for 5-OH-omeprazole, to be consistent with Simcyp™ built-in library model of omeprazole (Table 2). Indeed, the published PBPK model of esomeprazole considered that Cl_R was similar for both enantiomers and omeprazole is a racemic mixture. The esomeprazole model was introduced as a drug inhibitor in the current PBPK models.

Modeling of IL-6 profiles

In the present PBPK model, the IL-6 model used has been previously developed and validated.[30] A number of stimulations were performed to obtain different steady-state plasma IL-6 concentrations, and we found the one that matched the mean plasma IL-6 concentrations described in the cohort study at each day. The chosen mode of administration was an intravenous infusion of 30 doses of 9×10^{-5} μg/h with a 1-h interval. As previously described, the IL-6 compound built was linked to an effect on hepatic CYP3A and CYP2C19 levels, and new steady-state levels of these CYPs were achieved during the simulation period, and the suppressive effect of IL-6 on intestinal CYP was assumed to be the same as that on hepatic CYP.[31] The final parameters used to build the IL-6 compound for our PBPK model are shown in Table S2. Information on CYP3A4/5 and CYP2C19 inhibition by IL-6 was obtained by the reassessment of data contained in an in vitro study and not by directly using the values given in the existing IL-6 model.[32] The IL-6 model was introduced as a drug inhibitor in the current PBPK models.

Modeling of enzyme dynamics

The impact of IL-6 on CYPs was modeled as a suppression of CYP3A4/5 and CYP2C19 in the liver in the ADME simulator. The equation was revised from the literature and described previously.[30]

Plasma versus dried blood spot correlation

The ADME simulator gives concentrations of substances in plasma, whereas the concentrations obtained from the cohort study are in whole blood (dried blood spot [DBS]). Therefore, a correction factor had to be applied to covert the concentration obtained in DBS into plasmatic concentration. Raw data from a published study that assessed the correlation of the concentrations of probe drugs contained in the "Geneva cocktail" between plasma and DBS were used.[33] The following equations were used:

1. $[\mathrm{MDZ_{plasma}}] = [\mathrm{MDZ_{DBS}}] \times 1.581 - 0.031$
2. $[1-\mathrm{OH-MDZ_{plasma}}] = [1-\mathrm{OH-MDZ_{DBS}}] \times 1.790 - 0.048$
3. $[\mathrm{OMPZ_{plasma}}] = [\mathrm{OMPZ_{DBS}}] \times 1.413 + 1.126$
4. $[5-\mathrm{OH-OMPZ_{plasma}}] = [5-\mathrm{OH-OMPZ_{DBS}}] \times 1.562 - 0.315$

Development and validation of PBPK model to simulate the interaction between inflammation (IL-6) and CYP3A and CYP2C19 substrates

The current PBPK models (midazolam/1-OH-midazolam and omeprazole/5-OH-omeprazole) were developed with a stepwise strategy. First, plasma concentration–time profiles of midazolam and omeprazole and their respective main metabolites were simulated in a healthy Caucasian virtual population provided by the ADME simulator, with IL-6 as the inhibitor 1. A visual prediction check was performed to evaluate the accuracy of the PBPK model prediction. Then, omeprazole Vss was changed to better match the Vss found in the Caucasian population, and the esomeprazole model was integrated as the inhibitor 2 to optimize the simulation.

The model validation process was performed by comparing the model prediction of omeprazole and its main metabolite and esomeprazole with published studies conducted in healthy volunteers. Comparison of observed and simulated concentration-time profiles of omeprazole and its main metabolite, 5-OH-omeprazole, was performed using clinical data obtained from a study conducted in our laboratory by Bosilkovska et al. (raw data not shown).[19] The esomeprazole model also needed to be validated as a previously validated model was modified.[25] We extracted the concentration-time profile of esomeprazole from one study with the same dose used in the cohort study to obtain observational data.[34]

PK parameters were estimated by standard noncompartmental methods using WinNonlin Version 6.2.1 (Pharsight) and by Simcyp™.

Once these three substances were validated, the PBPK models prediction values were compared with the observed values in the cohort study between midazolam and omeprazole and their metabolites to assess its predictability and application.

All simulations were conducted using 10 trials containing 10 subjects for 8 days. Midazolam 1 mg and omeprazole 10 mg were administrated orally at 7 a.m. on Days 1, 2, 4, 6, and 7 (custom dosage) and esomeprazole 40 mg was administrated orally at 7 p.m. on Days 1, 2, and 3. A total of 30 doses of 9×10^{-5} μg with $\tau = 1$ h of IL-6 were administrated at 9 a.m. on Day 1. Simulated plasma concentrations of midazolam and omeprazole and their metabolites at 2 h, 26 h, 74 h, 122 h, and 146 h (to account for the 2 h required after the intake of midazolam and omeprazole) were compared with concentrations obtained at baseline, 24 h, and 72 h after surgery and at discharge (5 or 6 days after surgery).

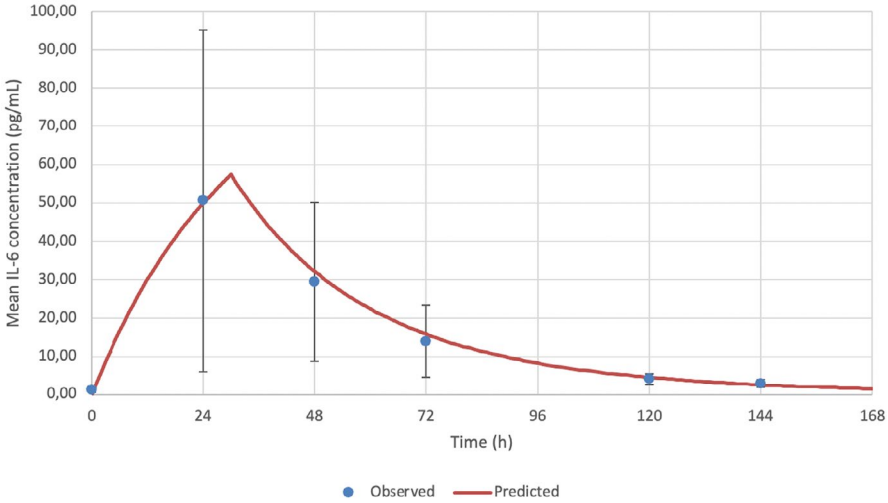

FIGURE 1 Observed concentration-time profile of IL-6 (dots) and simulated concentration-time profile of IL-6 (line). IL-6, interleukin-6

TABLE 3 Observed versus predicted pharmacokinetic parameters

	Observation	Simulation
IL-6		
Geometric mean AUC (mg.h/L)	0.0019 ± 0.0017	0.0018 ± 0.0007 (90% CI, 0.0017–0.0019)
Mean $t_{1/2}$ (h)	36.6 ± 14.7	32.6
Mean C_{max} (mg/L)	0.0001 ± 0.00004	0.0001 ± 0.00001
Omeprazole		
Geometric mean AUC (mg.h/L)	0.16 ± 0.14	0.22 ± 0.67 (90% CI, 0.186–0.267)
Mean $t_{1/2}$ (h)	1.03 ± 0.65	1.00 ± 1.15
Mean C_{max} (mg/L)	0.11 ± 0.05	0.15 ± 0.12
5-OH-omeprazole		
Geometric mean AUC (mg.h/L)	0.11 ± 0.026	0.22 ± 0.09 (90% CI, 0.211–0.239)
Mean $t_{1/2}$ (h)	1.25 ± 0.56	1.00 ± 1.14
Mean C_{max} (mg/L)	0.05 ± 0.02	0.14 ± 0.07
Esomeprazole		
Geometric mean AUC (mg.h/L)	3.87 (95% CI, 2.96–5.07)	4.11 (95% CI, 3.59–4.72)
Geometric mean $t_{1/2}$ (h)	1.25 (95% CI, 1.09–1.44)	1.35 (95% CI, 0.97–1.09)
Geometric mean C_{max} (mg/L)	1.60 (95% CI, 1.31–1.96)	1.14 (95% CI, 1.04–1.24)

Abbreviations: AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; IL-6, interleukin-6; $t_{1/2}$, 5-OH, half-life 5-hydroxy-omeprazole.

RESULTS

Model validation of IL-6 via prediction of clinical observation

The observed and simulated concentration-time profiles were compared, and the accuracy of the PBPK model prediction was confirmed (Figure 1). The simulated and observed PK parameters are presented in Table 3. The mean area under the curve (AUC) ratio between observation and simulation was 1.05, meaning that observation and prediction are similar.

Validation of the omeprazole and 5-OH-omeprazole models

The simulated and observed PK parameters are presented in Table 3, leading to a simulated geometric mean $AUC_{0-8\,h}$ ratio of 5-OH-omeprazole/omeprazole of 1.009. The observed geometric mean AUC ratio of 5-OH-omeprazole/omeprazole was 0.66.[19] Therefore, the AUC ratio between observation and simulation was 1.53, which is the accepted range of equivalence in PBPK modeling. PBPK models of omeprazole (Figure 2a) and 5-OH-omeprazole (Figure 2b) accurately predict the observed data. The slight

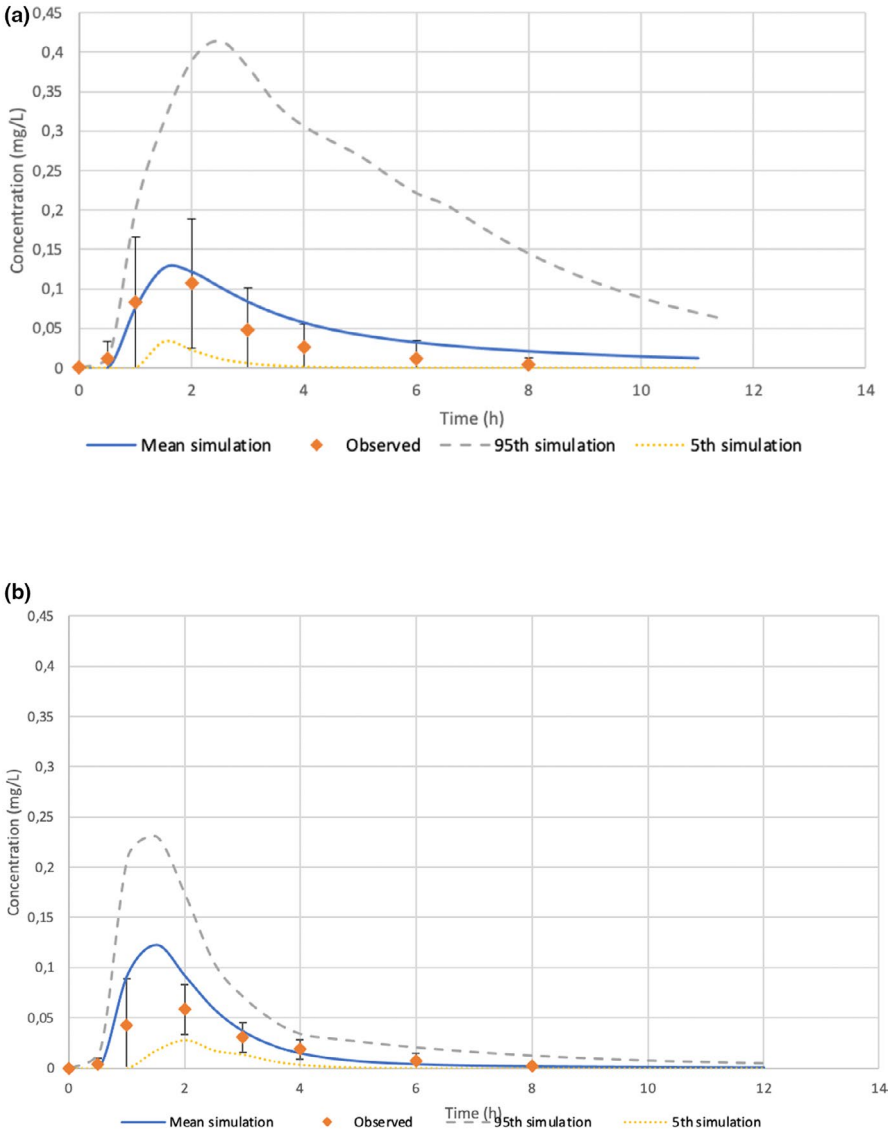

FIGURE 2 Observed concentration time-profile (dots) and simulated concentration-time profile (line) of (a) omeprazole and (b) 5-hydroxy-omeprazole

but acceptable overestimation of the simulated mean 5-OH-omeprazole concentrations could be explained by the sampling times of the training set where the point of the maximal concentration could have been missed. This was confirmed by the difference in maximum concentration (Table 3).

Validation of the esomeprazole model

Figure 3 shows the accurate prediction of the observed concentration-time profile of esomeprazole by the PBPK model.[34] The simulated and observed PK parameters are presented in Table 3. The geometric mean AUC ratio between observation and simulation was 1.06, which is in the accepted range of bioequivalence (between 0.85 and 1.25).

Verification of the performance of the PBPK models

The established PBPK models of midazolam/1-OH-midazolam and omeprazole/5-OH-omeprazole as well as those of esomeprazole and IL-6 were used to predict the effects of the mean IL-6 and esomeprazole concentration-time profiles on CYP3A and CYP2C19 activities in elective hip surgery patients. The changes in hepatic intrinsic clearance as a function of time of midazolam/1-OH-midazolam and omeprazole/5-OH-omeprazole, respectively, were thus simulated with the models. As three-quarters of the patients in the cohort study were on esomeprazole in the postoperative setting, an esomeprazole model was implemented in our PBPK models. Almost all patients took esomeprazole in the evening, so there was no interference with measuring the concentration of omeprazole

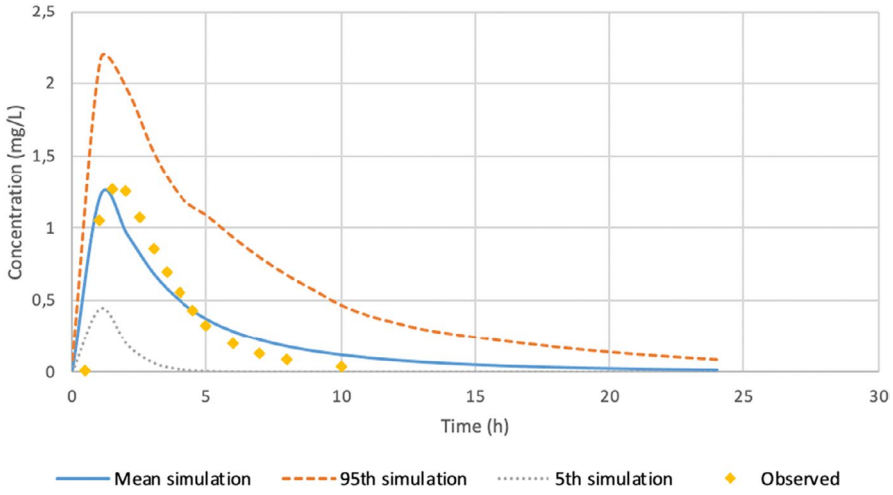

FIGURE 3 Observed (dots) and simulated (lines) concentration time-profiles of esomeprazole after 5 days of treatment with 40-mg esomeprazole

or 5-OH-OMPZ given in the morning to assess CYP2C19 activity. Indeed, esomeprazole is the S-isomer of omeprazole and the liquid chromatography with tandem mass spectrometry method used is unable to differentiate enantiomers, but its half-life is short, approximatively 1.3 h.[26] Moreover, about 27% of esomeprazole is metabolized in 5-OH-OMPZ, but its half-life is between 0.9 and 1.7 h, depending on CYP2C19 phenotype.[24,35]

Plasma concentrations of midazolam/1-OH-midazolam and omeprazole/5-OH-omeprazole at 2 h were simulated as a function of time-dependent changes in IL-6 and of esomeprazole intake. These simulated concentrations were comparable with those observed in the cohort study of elective hip surgery patients.[16] Indeed, as shown in Figure 4, the changes in the predicted mean concentrations as a function of time for midazolam (Figure 4a), 1-OH-midazolam (Figure 4b), omeprazole (Figure 4c), and 5-OH-omeprazole (Figure 4d) are within the accepted ratio of 2 to the mean observed concentration for 100% of simulated concentrations. Moreover, for 60%, 17%, 33%, and 33% of predicted mean concentrations for midazolam, 1-OH-midazolam, omeprazole, and 5-OH-omeprazole, respectively, the fold changes were less than 1.25, which is the limit of bioequivalence. The metabolic ratio (MR) versus time for midazolam (Figure 4e) and omeprazole (Figure 4f) were also within the accepted range. In addition, as shown in Figure S1, the observed mean concentrations 2 h after "Geneva cocktail" intake versus time were close to the simulated mean concentration versus time profile. The comparison between observation and prediction shown in Figure S1 can only be made with one observed time-point because it is a concentration obtained after phenotyping (MR 2 h after administration of the "Geneva cocktail"). Figure S2 shows that the time-varying IL-6 concentrations and esomeprazole intake decrease CYP3A and CYP2C19 activities. Moreover, CYP2C19 activity without both inhibitors was not 100% during the first days of the study because omeprazole was administrated periodically until Day 7 to assess CYP2C19 activity and it inhibits its own metabolism. CYP2C19 and CYP3A activity returned to 100% when no further CYP2C19 and CYP3A inhibitors were administered to patients. Indeed, esomeprazole and the probe drugs (midazolam and omeprazole) were no longer administered after Day 3 and Day 7, respectively, and IL-6 levels gradually decreased (Figure 1). A return to baseline could therefore be expected after approximatively 12 days (Figure S2).

Comparing simulated drugs concentrations with and without drug-drug interactions (esomeprazole) and drug–disease interactions (IL-6) in the investigated clinical studies obtained at every hour throughout the study, there were 2.1 ± 0.3-fold, 1.6 ± 0.2-fold, 3.1 ± 0.6-fold, and 3.2 ± 0.6-fold (mean ± SD) increases in simulated concentrations of midazolam, 1-OH-midazolam, omeprazole, and 5-OH-omeprazole, respectively.

DISCUSSION

A virtual surgery population was developed and validated to assess the impact of surgery as a source of variability in drug effects and to predict the changes in the PK profiles of concomitant treatments in the postoperative setting. We used observed data from a real-life study conducted in our center in elective hip surgery, where CYP activities were evaluated using a cocktail approach to build the model.[16]

The prediction of IL-6-mediated drug–disease interaction via PBPK modeling had been previously described in the literature.[30,31,36–39] Indeed, PBPK models were developed to predict the impact of elevated levels of IL-6 on CYP substrates using a cocktail approach

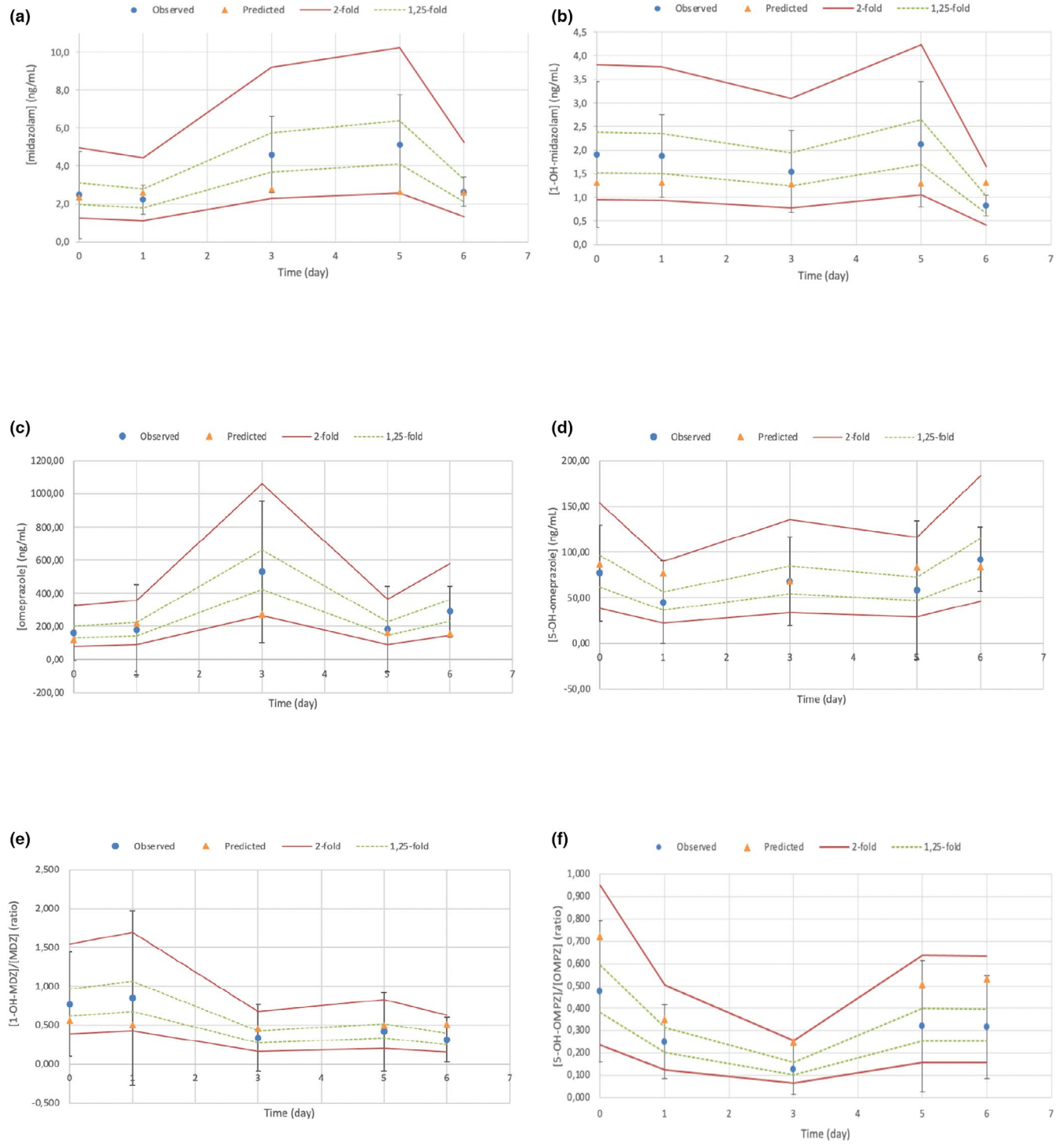

FIGURE 4 Concentration versus time profiles (a-d) and metabolic ratio vs time profiles (e-f) for observed and predicted values and corresponding fold changes of 2 (lines) and 1.25 (dashed lines), 2 h after "Geneva cocktail" intake in the presence of time-varying interleukin-6 concentrations and esomeprazole intake for (a) midazolam, (b) 1-hydroxy-midazolam, (c) omeprazole] (d) 5-hydroxy-omeprazole, (e) 1-hydroxy-midazolam/midazolam, and (f) 5-hydroxy-omeprazole/omeprazole

with probe drugs or assessing simvastatin, rivaroxaban, and vancomycin PK in different special populations (rheumatoid arthritis, neuromyelitis optica, or critically ill sepsis).[30,31,36–39] They used in vitro data to quantitatively predict the intensity of the clinical drug–disease interaction via IL-6, which appears to be the key element in modulating CYP activities during inflammation.[7,32,37,40,41]

In our study, PBPK models were developed for omeprazole and midazolam and their main metabolites using

whole-blood (DBS) data and drug-specific correction factors to convert DBS to plasma concentrations.[33] Indeed, Simcyp™ uses the plasma concentration. To our knowledge, this is the first time that concentrations from whole blood have been used in Simcyp™.

We confirmed that omeprazole by default (from the Simcyp™ built-in library) does not match the Caucasian population.[19] According to the literature, the Vss of omeprazole varies with the ethnicity of the population.[21] Our observed data population study was Caucasian, so the Vss value was changed accordingly from 0.15 L/kg to 0.23 L/kg.[20,21] Our new model was consistent with the values observed in the literature.[19]

As our cohort study did not give complete PK of midazolam and omeprazole, it was important to build a model for the main metabolites of midazolam and omeprazole to increase the confidence and predictability of the developed models.

Midazolam is mainly metabolized by CYP3A to 1-OH-midazolam.[22] We used a previously published and validated model of 1-OH-midazolam.[23]

Omeprazole is mainly metabolized in 5-OH-omeprazole by CYP2C19, and we thus designed a model for 5-OH-omeprazole into the current PBPK model.[24] We adapted an existing model by changing the Cl_R as it was assumed that 5-OH-omeprazole Cl_R was the same as that of omeprazole.[25] This new 5-OH-omeprazole plasma concentration is consistent with data observed in the literature.[19]

Esomeprazole is a well-known CYP2C19 inhibitor that was systematically prescribed in our cohort study to prevent the occurrence of stress ulcer, although we would have liked to exclude all CYP modulators.[26] To simulate the impact of inflammation attributed to surgery on CYP2C19 activity, we thus considered CYP2C19 inhibition by esomeprazole.

As with omeprazole, we changed the Cl_R to 0 L/kg. The published model for esomeprazole used both a mechanism-based and a reversible CYP3A inhibition by esomeprazole.[25] We removed the mechanism-based inhibition of CYP3A by esomeprazole, leaving only reversible inhibition as the literature does not report irreversible inhibition of CYP3A by esomeprazole.[28,29] Based on the validation results, our esomeprazole model was consistent with the data observed in the literature.

The disease–drug interaction is complex and depends on a multitude of factors that are not always known, making in vitro–in vivo extrapolation difficult. Indeed, studies have reported that the onset of inflammation impacts the levels of other proteins than cytokines and that they influence the PK parameters of drugs.[10,42,43] Also, some evidence suggest that cytokines may modulate the transporter activities that also play a role in the ADME process.[10,42] Moreover, DDIs have multiple sources, as multiple PK and pharmacodynamic (PD) factors can interfere.[25] PBPK modeling can help evaluate DDIs without clinical trials and is used in drug development.[44,45]

Our model has allowed the innovative integration of a PD biomarker, IL6, as a marker of inflammatory response. The development and use of PBPK models go beyond the prediction of PK properties of a drug as they have been used to predict and assess drug efficacy and safety.[46] Other perspectives are to combine PK models with the corresponding PD response as we have successfully done in our model.[46,47] Our PBPK approach successfully predicted the modulation of CYP3A and CYP2C19 activities by IL-6 (drug–disease interaction) and esomeprazole (DDI). Improvements will, however, have to be made to bring all predicted values within this bioequivalence range to introduce it into clinical practice. These simulations showed the importance of this type of approach to support personalized medicine, as the interactions increased midazolam and omeprazole concentrations by twofold and threefold, respectively, which may lead to efficacy and safety concerns. Because of the increase in life expectancy, patients are medically more complex due to a greater number of comorbidities and, consequently, comedications.[48] Model-informed precision dosing (MIPD) allows for the prediction and selection of the correct dose considering the contribution of covariates to reduce the variability of a target concentration as clinicians must deal with variability in many ways.[48] The development of MIPD could fulfill the need in clinical practice to facilitate interpretation and decision making toward the abundance and complexity of data in clinical care, such as complex drug-drug-gene-disease interactions influencing drug efficacy and safety.[48]

Smart, easy-to-use, and clinically validated MIPD tools could integrate all of these factors and enable optimal drug use, leading to the improvement of health outcomes, decrease of drug-related harm, and smaller economic burden.[48] To the best of our knowledge, our PBPK models are the first models to include both DDI and the drug–disease interaction, and this is a step forward in the development and use of MIPD to achieve precision medicine. In addition, these PBPK models may be useful to complement those developed in emerging therapeutic areas, such as chimeric antigen receptor T (CAR-T) and T cell–redirecting bispecific antibody therapy, as patients have also reported temporary elevation of cytokines, including IL-6, following treatments.[37,49] This approach has the potential to be extended to provide dosing guidance for concomitant medications during such treatments.

Our study has some limitations. First, the data used to inform the PBPK model of in vitro IL-6 suppression of CYP3A and CYP2C19 came from a single study. Moreover, our model only considered the suppressive effect of IL-6

and not the impact of other cytokines or acute-phase proteins such as C reactive protein. However, as mentioned previously, IL-6 is considered to be the critical cytokine responsible for the downregulation of CYP activities. This suggests that incorporation of other inflammatory biomarkers would result in only minor changes. Another important limitation is that we used clinical data from a study that was not designed to provide complete concentration-time profiles, but only the concentrations of probe substrates 2 h after oral administration. It would have been more accurate and meaningful to compare concentration-time profiles between simulated and observed data. In an attempt to compensate for the lack of comparators, we also simulated the major metabolites of midazolam and omeprazole produced by CYP3A and CYP2C19, respectively. Another limitation inherent in the cohort study was that the follow-up period was not long enough to see a return to baseline levels of CYPs. Indeed, the majority of included patients were discharged from the hospital 3 days after surgery and never more than 6 days after.[26] Finally, it was not possible to discriminate between the inhibitory effect of IL-6 or esomeprazole on CYP2C19 because it was a routine postoperative treatment.[26]

CONCLUSION

Inflammation is a transient or chronic health condition, inducing transient or chronic physiopathological changes, which may impact on drug PK parameters. PBPK simulations allow varying system parameters and incorporating literature-based alterations in CYP activities due to inflammation. The current model successfully predicted midazolam and omeprazole and the PK of their main metabolites in a population with surgery-related acute reversible inflammation. Moreover, the integration of the esomeprazole model resulted in a better fit for omeprazole PK. This study could be a basis for refining dosing recommendations in the postoperative setting, especially in drugs with narrow therapeutic indexes. In fact, PBPK models may be an effective and efficient way to investigate the risk of interaction using existing knowledge about the distinctive characteristics of the disease population. The integration and prediction of PD and disease parameters in PBPK models thus appears to be a promising approach to personalize treatments.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

C.L., Y.D., and C.F.S. wrote the manuscript. C.L., A.N., V.R., J.A.D., Y.D., and C.F.S. designed the research. C.L. and A.N. performed the research. C.L., A.N., Y.D., and C.F.S. analyzed the data. C.L., A.N., and Y.D. contributed new reagents/analytical tools.

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