

Research Article

Feasibility of a Web-Based Visualization Tool for Estimating Ibuprofen Pharmacokinetic and Pharmacodynamic Profiles to Support Self-Medication

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Abstract

Background: Ibuprofen is an over-the-counter (OTC) medication widely used as an antipyretic and analgesic. However, frequent use without medical supervision can lead to improper use and unintended side effects. Nonetheless, obtaining advice from medical professionals regarding OTC drugs can be difficult for ordinary users. Hence, this study aimed to develop a user-friendly visualization-based web application for ibuprofen and to verify the feasibility of enabling general users to simulate and visualize blood drug concentrations and predict drug efficacy, thereby informing proper usage. **Methods:** Previously reported population pharmacokinetic and pharmacodynamic (PK/PD) models were reconstructed using Phoenix® NLME, and the estimates were validated via visual predictive check against reported population observations and values derived from physiologically based pharmacokinetic (PBPk) analysis. Additionally, to facilitate visualization of the effects of ibuprofen on the body, a web application for PK/PD simulation was developed based on the reconstructed model and implemented in Python using the Runge–Kutta method. **Results:** The developed web application (VisiblePharm™) visualized the relationship between the administered dose and ibuprofen concentration in plasma over time and simultaneously assess its efficacy. However, individual differences are limited to variations resulting from differences in physique. The simulation results also showed good agreement with estimates derived from PBPk analysis. **Conclusion:** VisiblePharm demonstrated that, despite the use of a limited set of covariates within the reconstruction model, it is possible to readily estimate the pharmacokinetics and antipyretic effects of ibuprofen following administration. We believe that with further clinical validation, this application will contribute to society as a health planning support tool, facilitating successful self-medication.

Keywords: ibuprofen; pharmacokinetics; nonlinear dynamics; patient simulation; data visualization; health planning support

1. Introduction

Many commonly used medicines are taken without supervision by medical professionals, and unexpected side effects or inappropriate use can occur. Ibuprofen, a widely used drug, is commonly administered for pain and fever [1]. It is a non-steroidal anti-inflammatory drug (NSAID) approved for over-the-counter (OTC) use [2]. Therefore, ibuprofen is one of the medicines selected for self-medication as an antipyretic or analgesic. The recommended dose is 200 mg for a single dose and up to 1200 mg per day [3].

Improper use of ibuprofen can lead to serious adverse events (AEs), which are dose- and duration-dependent [2]. Currently, a large number of people self-medicate using ibuprofen because they believe it is safe as a result of the coronavirus disease 2019 (COVID-19) epidemic. However, the safety of ibuprofen remains under investigation [4,5]. The AEs of ibuprofen frequently involve the gastrointestinal (GI) tract; for example, GI tract bleeding and/or perforation [6]. Serious GI AEs may occur with high

doses and long-term use [2]. Several reports showed that overdosing on ibuprofen leads to severe toxicity and can contribute to death [6,7]. Although ibuprofen is categorized as an OTC drug, it can significantly affect individuals with ulcers, and body weight, age, and gender are covariate risk factors [2,8].

Several population pharmacokinetic (PK) and pharmacodynamic (PD) models for ibuprofen have been reported [9,10,11]. In a population PK/PD model, individual observed data are described in relation to the population averages while considering individual differences [12]. Therefore, these models provide information about the ibuprofen dose range and covariate factors that influence the PK profile and contribute to the PD profile and are very useful for describing the proper use of ibuprofen. However, a user-friendly and interactive tool for predicting the appropriate use of ibuprofen, for example, estimating the concentration and efficacy, does not yet exist.

Therefore, using a previously established population PK/PD parameter model, this study aimed to verify the fea-



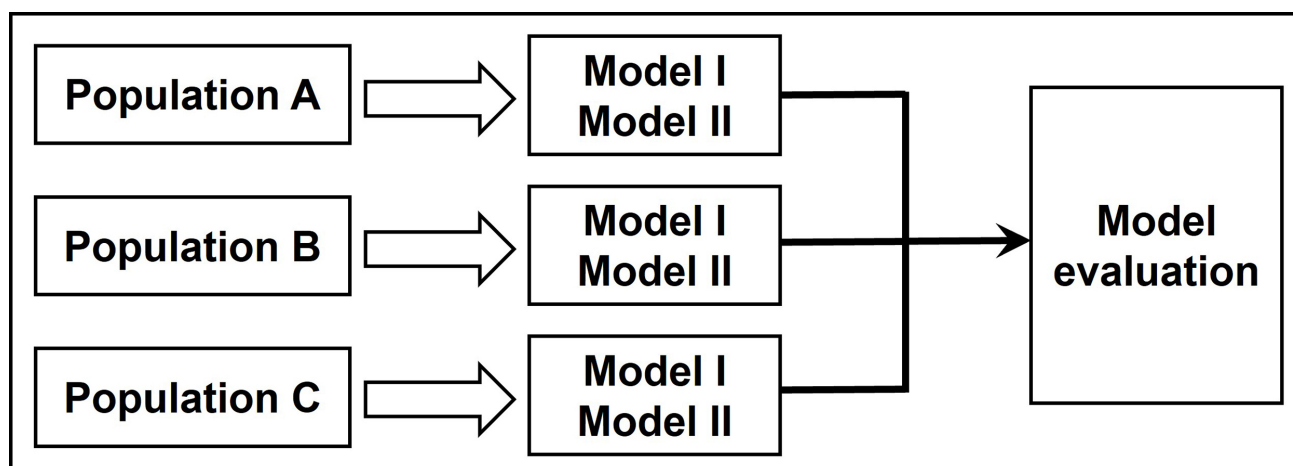


Fig. 1. Workflow for model comparison. Model I is the PK model of Morse et al. [10] and model II is from Trocóniz et al. [9]. Populations A, B, and C are the virtual populations of Hattrem et al. [13], Shin et al. [14], and Sugár et al. [15], respectively.

sibility of a visualization-based web application to simulate ibuprofen concentration in the body together with a prediction of its efficacy. The model was selected from among several population PK/PD models to achieve reliable simulation results and PK/PD profile predictions. In addition, the easy visualization feasibility of estimating the antipyretic and analgesic efficacy of ibuprofen using the selected PK/PD models was evaluated. The results of this study will promote a simple and practical method for determining the proper use of ibuprofen to achieve successful self-medication.

2. Materials and Methods

2.1 Population PK Model Comparison

Two population PK models of ibuprofen [9,10], together with their previously established population characteristics, were reproduced. The PK model of Morse et al. [10] was designated as model I, and that of Trocóniz et al. [9] as model II. Virtual populations based on Hattrem et al. [13], Shin et al. [14], and Sugár et al. [15] were designated as populations A, B, and C, respectively. Each model was reproduced by extracting the compartmental model structure, population PK parameter estimates, covariate model, inter- and intra-individual variability, and estimation method from the original studies. The modelling process was performed and simulated using Phoenix® NLME 8.4 (Certara USA, Inc., Princeton, NJ, USA) for the non-linear mixed effect modeling (NONMEM) analysis. The PK profiles were compared across models, and populations A, B, and C were used to assess the model using visual and numerical evaluation (Fig. 1, Ref. [9,10,13,14,15]). The best-fit model was selected by considering a visual predictive check (VPC), the visual goodness-of-fit, and root mean square error (RMSE) [16,17]. The goodness-of-fit and compatibility of the model with various characteristics of the population were used to select the best model.

2.2 Generation of the Virtual Population

A virtual patient population of 100 individuals for each model and population characteristics taken from the literature (populations A, B, and C in Fig. 1) [13,14,15] was created using Monte Carlo simulations to validate the PK models. The PK model of Morse et al. [10] was indicated as model I and one of Trocóniz et al. [9] as model II. Virtual population of Hattrem et al. [13] was indicated as population A, Shin et al. [14] as B, and Sugár et al. [15] as C. For the PD analysis, the study populations were defined as follows: Trocóniz et al. [9] was used for the temporal changes in body temperature in children administered ibuprofen (pediatric febrile population), Smith et al. [18] was used for temporal changes in body temperature in adults (adult febrile population), and Li et al. [11] was used for the temporal changes in pain relief scores for dental pain following ibuprofen administration (dental pain population). Because height was not reported in the pediatric febrile population, it was calculated as the square root of (body weight/22) in the virtual population generation. In the adult febrile population, neither height nor body weight was reported—only body mass index (BMI) was provided—and hence a simulated population based on BMI was first randomly generated. Next, body weight in the range of 55–85 kg (with a mean of 70 kg) were randomly generated, and height was calculated as the square root of (body weight/22). Additionally, because Li et al. [11] provided no demographic data other than the number of subjects, the virtual population from the adult febrile population dataset was used. For each study population, a virtual cohort consisting of 100 individuals was randomly generated using the demographic characteristics reported in the corresponding studies. The population means over time for each of the reported clinical trials were obtained using Engauge Digitizer (version 12.1).

Table 1. Ibuprofen population pharmacokinetic parameters estimated for two models.

Parameter	Model I (Morse et al. [10])		Model II (Trocóniz et al. [9])	
	Estimate	CV (%)	Estimate	CV (%)
CL (L/h/70 kg)	3.79	22.1	4.05	24
Q (L/h/70 kg)	10.5	66.0	2.09	46
V1 (L/70 kg)	6.05	30.2	4.4	NE
V2 (L/70 kg)	4.37	53.0	6.62	65
Ka (h ⁻¹)	1.56	78.7	0.82	31
T _{LAG} (h)	0.111	80.9	none (for suspension)	16
RE _{ADD} (mg/L)	0.422			
RE _{PROP} (%)	24.0		11.0	

CL, total plasma clearance; Q, intercompartmental clearance; V1, volume of distribution of the central compartment; V2, volume of distribution of peripheral compartment; Ka, first-order rate constant of absorption for ibuprofen tablet; T_{LAG}, lag time; RE_{ADD}, additive residual variability; RE_{PROP}, proportional residual variability; CV, Coefficient of Variation; NE, not estimated.

2.3 Pharmacokinetic Modelling Reproduction

The model I is briefly described below. It was constructed as a two-compartment disposition model parameterized using elimination clearance (CL) from the central compartment, intercompartmental clearances (Q), central (V1) and peripheral (V2) volumes of distribution, absorption rate constant (Ka), and lag time (T_{LAG}). The coefficient of variation (CV) of the population parameter was accounted for using an exponential model for the random effect variables (η).

$$P_i = P_{pop} e^{\eta_i} \quad (1)$$

where P_i is the parameter for the i th individual, and P_{pop} is the population parameter estimate for parameter P (CL, Q, V1, V2, Ka, T_{LAG}). Moreover, CL_{pop} is expressed by the following equation:

$$CL_{pop} = CL_{STD} \times \left(\frac{A \times HT^2 \times \left[\frac{TBM}{(B \times HT^2 + TBM)} \right]}{56.1} \right)^{3/4} \quad (2)$$

Here, the subscript STD denotes the value of each standardized parameter. For the other parameters, the population parameter estimates were identical to the STD values. Moreover, total body mass (TBM) indicates total body mass (kg) and height (HT) indicates height (m) as covariates. A and B are lipid-related factors that differ by gender; for men, A was 42.92 and B was 30.93; for women, A was 37.99 and B was 35.98. Intra-individual variation was treated as both an additive residual error (RE_{ADD}) and proportional residual error (RE_{PROP}).

Model II was also constructed as a two-compartment disposition model parameterized using CL, Q, V1, V2, Ka, and T_{LAG}. Since the final version of model II was based on the suspension formulation, the conversion factors be-

tween the suspension and tablet forms reported for Model I were applied (0.719 for suspension relative to 1 for a tablet for 1/Ka, and 0.984 for T_{LAG}). Additionally, because T_{LAG} was not originally included in model II for suspension, the T_{LAG} value from model I was used in model II. The CV of the population parameter was an exponential model for the random effect variables (η) as follows:

$$P_i = (P_{pop} \cdot TBM_i/70) \cdot e^{\eta_i} \quad (3)$$

$$P_i = (P_{pop} \cdot TBM_i/70)^{3/4} \cdot e^{\eta_i} \quad (4)$$

where P_i is the parameter for the i th individual, and P_{pop} is the population parameter estimate for the parameter P (V1, V2, Ka, T_{LAG}) in Eqn. 3 and P (CL, Q) in Eqn. 4. Intra-individual variation was treated as proportional residual errors (RE_{PROP}). The parameter evaluation values for models I and II are summarized in Table 1 (Ref. [9,10]).

2.4 Pharmacodynamic Modelling Reproduction

The final model [9] describing changes in body temperature over time following ibuprofen administration was the following inhibitory sigmoidal Emax model:

$$\frac{dT}{dt} = k_{syn} \cdot \left(1 - E_{max} \frac{C^n}{C^n + EC_{50}^n} \right) - k_{out} \cdot T \quad (5)$$

where dT/dt represents the rate of change in body temperature, k_{syn} is the zero-order formation rate constant of the effector, k_{out} is the first-order degradation rate constant of the effector, T is body temperature, E_{max} is the maximum drug effect, EC_{50} is the plasma drug concentration (C) eliciting half of the maximum effect, and n is the slope of the K_{syn} versus C relationship. This model incorporates the following relational expression, with T₀ as the initial body temperature: $k_{syn} = k_{out} \cdot T_0$.

Table 2. Ibuprofen population pharmacodynamic parameters reported for fever and dental pain models.

Parameter	Fever (Trocóniz et al. [9])		Dental pain (Li et al. [11])	
	Estimate	CV (%)	Estimate	CV (%)
EC ₅₀ (mg/L)	6.18	62	10.20	NE
k _{out} (h ⁻¹)	1.17	78		
E _{max}	5.50 × 10 ⁻²	25	1.80	105.4
T ₀ (°C)	38.80	0.8	-	-
n	2.71	-	2.00	-
P _{max}	-	-	1.54	114.0
K (h ⁻¹)	-	-	1.26	1.2
K _{eo} (h ⁻¹)	-	-	1.49	14.0
RE _{ADD} (mg/L)	NE	NE	0.51	-

EC₅₀, plasma drug concentration eliciting half the maximum effect; k_{out}, first-order rate constant of degradation of the effector; E_{max}, maximum drug effect; T₀, initial body temperature; n, steepness of the relationship; P_{max} (pain relief unit), maximum placebo pain relief effect; K, first-order rate constant of placebo effect; K_{eo}, first-order equilibration rate constant; RE_{ADD}, additive residual variability; CV, Coefficient of Variation; NE, not estimated; -, not included in the analysis.

The final model [11] describing changes in the pain relief over time following ibuprofen administration was the following sigmoid-Emax model:

$$f(t) = P_{max} \cdot (1 - e^{-Kt}) \quad (6)$$

$$f(C_e) = \frac{E_{max} \cdot C_e^n}{C_e^n + EC_{50}^n} \quad (7)$$

$$\frac{d(C_e[t])}{dt} = K_{eo} \cdot (C[t] - C_e[t]) \quad (8)$$

where P_{max} represents the maximum placebo pain relief effect, K is the first-order rate constant of placebo effect, E_{max} is the maximum pain relief produced by ibuprofen, EC₅₀ is the plasma drug concentration at half-maximal effect, and n is the steepness of the relationship, C_e is the effect-site ibuprofen concentration, K_{eo} is the first-order equilibration rate constant. The parameter evaluation values for the PD modelling are summarized in Table 2 (Ref. [9,11]).

2.5 Development of a Visualization Web-Application

The developed web application, called VisiblePharmTM, was developed to provide an interactive framework so the user can easily input their data (body weight, height, and body temperature immediately before using ibuprofen) and the dose of ibuprofen. The application will simulate the drug concentration and present the effect profile through graphical visualizations.

This application consists of a web server, HTML documents to generate the input and result pages, a Python 3.6.15 script (**Supplementary Material**) for personalized

estimation, and the Matplotlib library for creating diagrams. PK estimation following ibuprofen administration was performed using the Runge–Kutta method in Python for the dynamic simulations. The Runge–Kutta method was implemented using the RK45 algorithm in the Solver module of SciPy 1.10.1; the step size was automatically calculated and averaged 0.57.

2.6 Comparison Between Populations Using Physiologically Based Pharmacokinetic Modelling

The Simcyp® simulator V24.0.368.0 (Certara Ltd., Sheffield, UK) was used to evaluate the pharmacokinetic parameters of populations using physiologically based pharmacokinetic (PBPK) modelling. Ten trials with 10 subjects in each trial were conducted for a single oral administration of 200 mg of ibuprofen in each population aged 35 to 55. The ibuprofen settings were based on the substrate parameters reported [19] and were as follows. The molecular weight was 206.7, log P was 3.23, compound type was a monoprotic acid, solubility at pH 1.2 was 0.038 mg/mL, and pK_a was 4.5. Moreover, the absorption model used was Advanced Dissolution, Absorption, and Metabolism (ADAM); P_{eff,man} was 6.309 (10⁻⁴ cm/s), P_{app,Caco-2} (10⁻⁶ cm/s) was 53, and K_a was 2.596 (h⁻¹). The distribution model was Full PBPK, with a V_{ss} of 0.120 (L/kg); for elimination, specificities regarding CYP isoforms were set based on reported data.

2.7 Statistical Analysis

Correlation analysis between observed population values and estimates derived from the dynamic model was performed using SigmaPlot (version 14.1) with Pearson correlation. VPC between observed population values and estimates derived from the population PK/PD models was performed using Phoenix NLME 8.4.

Table 3. Demographic statistics for the previously reported group and the newly generated population corresponding to them.

Population	Attribute	Reported demographics	Randomly generated demographics
Population A [13]	N	20	100
	Age	29.0 ± 7.8	-
	HT	177.1 ± 5.4	177.1 ± 4.8
	TBM	69.3 ± 8.6	70.3 ± 6.6
	BMI	22.1 ± 2.7	-
	Female:Male	0:1	0:1
Population B [14]	N	36	100
	Age	25.0 ± 3.0	-
	HT	175.1 ± 6.1	174.9 ± 5.53
	TBM	70.3 ± 7.9	69.8 ± 6.8
	BMI	22.9 ± 2.2	-
	Female:Male	0:1	0:1
Population C [15]	N	32	100
	Age	27.1 ± 7.6	-
	HT	174.8 ± 9.6	172.6 ± 3.7
	TBM	76.79 ± 13.606	73.5 ± 9.0
	BMI	24.97 ± 2.804	-
	Female:Male	11:21	17:33
Pediatric febrile [9]	N	52	100
	Age	8.5 (4–16)	-
	HT	NR	121.2 ± 16.9
	TBM	32.5 (25–59)	32.5 ± 9.7
	BMI	NR	-
	Female:Male	24:28	43:57
	BT	39.1 (38.0–40.2)	39.1 ± 0.6
Adult febrile [18]	N	83	100
	Age	32.3 ± 10.4	-
	HT	NR	163.7 ± 17.6
	TBM	>50 kg	71.6 ± 8.9
	BMI	27.8 ± 4.1	27.2 ± 4.4
	Female:Male	0:1	0:1
Dental pain [11]	N	22	100
	Age	16–40	-
	HT	NR	163.7 ± 17.6
	TBM	NR	71.6 ± 8.9
	BMI	NR	27.2 ± 4.4
	Female:Male	NR	0:1

N, number of people; HT, height (cm); TBM, total body mass (kg); BMI, body mass index; BT, baseline body temperature (°C); NR, not reported; Reported demographic data are presented as mean and standard deviation or mean and range. Randomly generated demographic data are presented as mean and standard deviation for the attribute used in the simulation.

3. Results

3.1 Virtual Population

For each study population, a virtual cohort consisting of 100 individuals was generated by Monte Carlo simulation using the mean and standard deviation, or the mean and range of the demographic characteristics reported in the corresponding studies (Table 3, Ref. [9,11,13,14,15,18]).

3.2 Population PK Model Comparison and Evaluation

In the reported clinical trials, a single oral dose of the 100 mg ibuprofen tablet was administered to population A [13], a 200 mg tablet to population B [14], and a 400 mg tablet to population C [15]. The pharmacokinetics for virtual populations A, B, and C were simulated using models I and II with ibuprofen doses matching those in the respective trials, and the simulated results were compared with the observed population mean values using VPCs (Fig. 2). For all

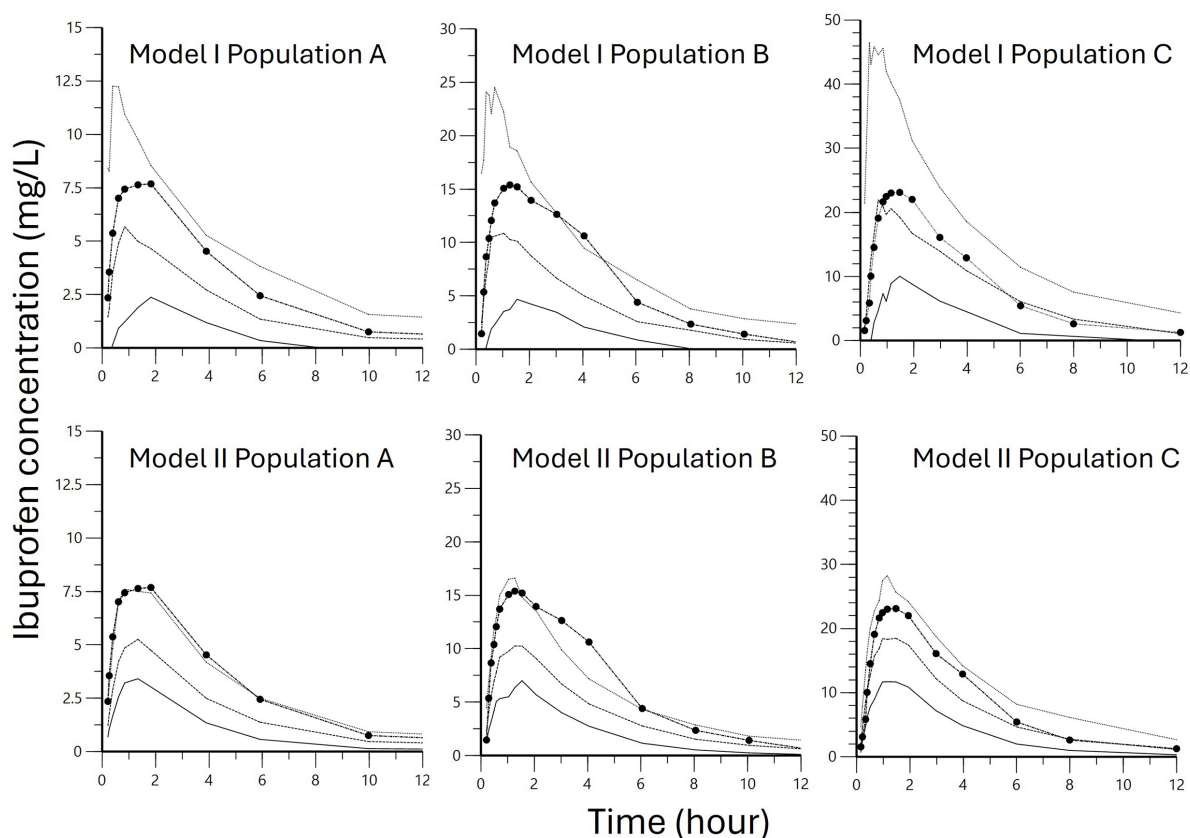


Fig. 2. VPC of ibuprofen pharmacokinetic values using models I and II and observed population means. A single oral dose of a 100-mg ibuprofen tablet was administered to Population A, a 200-mg tablet was administered to Population B, and a 400-mg tablet was administered to Population C. Solid lines indicate the 5th percentile of the estimated blood concentration of ibuprofen, dash lines the 50th percentile, and dotted lines the 95th percentile. Solid circles indicate the reported population means over time. VPC, visual predictive check.

three populations, the observed population mean values for ibuprofen blood concentrations over time were within the 90% prediction interval (5th–95th percentile range) when using model I except for a four-hour period for population B. In Model II, the observed values were within the 90% prediction interval only for simulated population C. Furthermore, a correlation analysis between the observed values and the estimated values from models I and II revealed a correlation coefficient of 0.947 ($p < 0.01$), a coefficient of determination of 0.897 and an RMSE of 2.997 for model I, and a correlation coefficient of 0.917 ($p < 0.01$), a coefficient of determination of 0.840 and an RMSE of 2.973 for model II (Fig. 3). Although the RMSE for the estimates based on model II was slightly lower than that for model I, the VPC and correlation coefficients suggested that model I demonstrated a better goodness-of-fit across multiple trials regarding pharmacokinetic estimation following ibuprofen administration.

3.3 Assessment of Simulated Population in PK/PD Model

Based on the study by Trocóniz et al. [9] on body temperature changes in children following a 7 mg/kg dose of

ibuprofen, a virtual pediatric febrile population was generated; similarly, a virtual adult febrile population was created using data from Smith et al. [18] on temperature changes in adults following administration of 250 mg ibuprofen, and a dental pain virtual population was developed based on findings by Li et al. [11] describing the analgesic effects of ibuprofen on dental pain in adults following administration of 400 mg ibuprofen. Using these populations, pharmacokinetic modelling using model I and pharmacodynamic modelling were performed to generate estimates, and the validity of the estimates over time was evaluated (Fig. 4). For the antipyretic effect of ibuprofen, the observed population mean values fell within the 5th–95th percentiles of the estimated values for both children and adults. As for the dental pain relief scores, although the observed population mean values fell within the 5th–95th percentiles of the estimated values, the estimated values might indicate a false-positive result regarding the relief effect.

3.4 VisiblePharm Web Application

After it was confirmed that the population PK/PD model was able to accurately estimate the effects of ibupro-

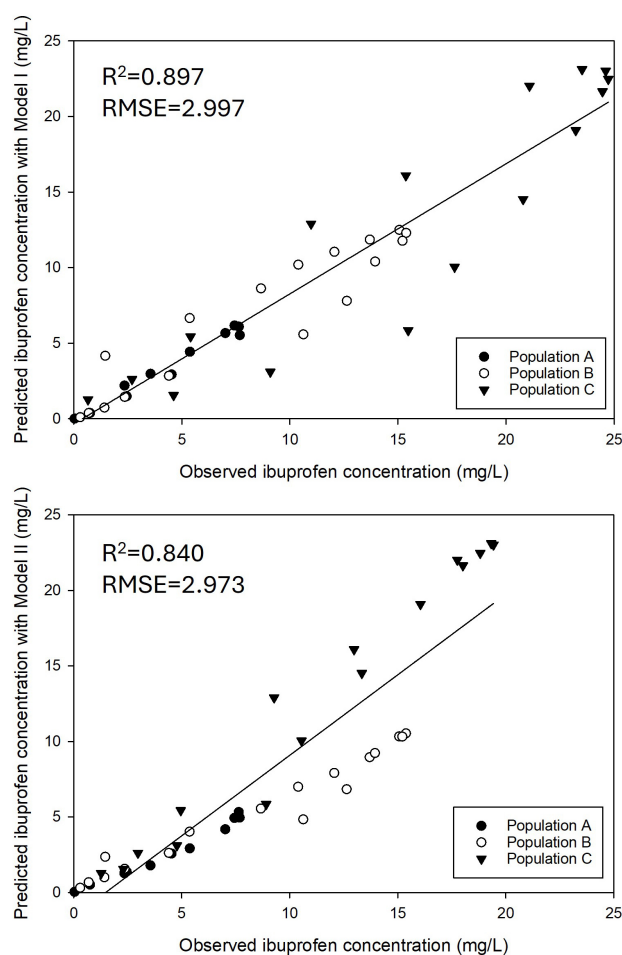


Fig. 3. Relationship between the observed and estimated values from models I and II for populations A, B and C. The coefficient of determination R^2 was calculated using the correlation coefficient with Pearson correlation. RMSE was calculated by averaging the squared differences of the predicted and observed values and taking the square root of the result. RMSE, root mean square error.

fen in a hypothetical patient population, the visualization method (VisiblePharm) was constructed to visualize the effects of ibuprofen on the body. The goal of this study was to create a website that enables the public to easily determine when the effects and side effects of this drug will appear. To achieve this, we developed the website using Python. A server with sufficient capacity was required to perform calculations quickly, and hence ConoHa WING, a web hosting service, was used. If a server is set up on an intranet instead of using a web hosting service—wherever appropriate—it becomes possible for companies or hospitals to operate websites without the risk of personal information leakage.

Since model I demonstrated better performance regarding the VPC and the correlation between estimated values and observed population data, we adopted model I and the antipyretic effect—which was deemed estimable via VPC—as the PD endpoint. We then proceeded to develop

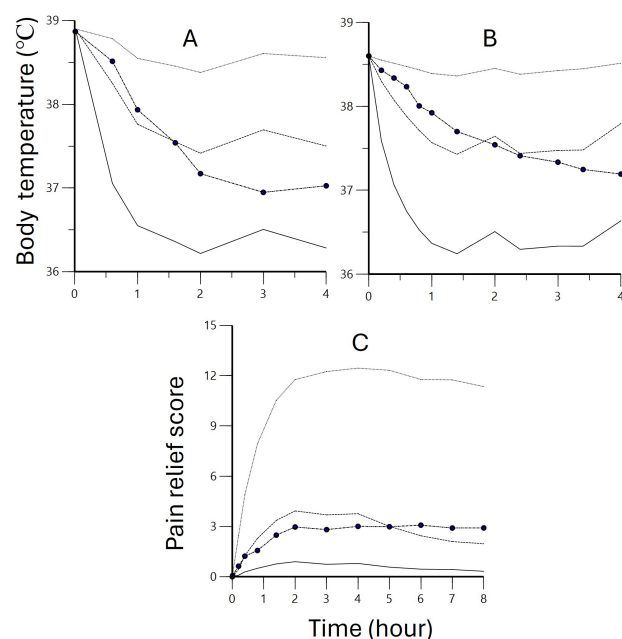


Fig. 4. VPC of ibuprofen pharmacodynamic values using pharmacokinetic model I and observed population means. (A) Estimated body temperatures and observed population means for the febrile pediatric population following administration of 7 mg/kg ibuprofen tablets. (B) Estimated body temperatures and observed population means for the febrile adult population following administration of 250-mg ibuprofen tablets. (C) Estimated dental pain relief scores and observed population means for the dental pain population following the administration of 400-mg ibuprofen tablets. Solid lines indicate the 5th percentile values, dashed lines the 50th percentile values, and dotted lines the 95th percentile values for the changes in body temperature over time (A and B) and the pain relief score (C). Solid circles reported the population means over time.

a web application for visualization that incorporates longitudinal PK/PD estimation.

Users are required to input their dose, weight, height, gender, and the initial body temperature. However, regarding gender, given the current social context, the option to make no selection was permitted. In such cases, “female” is automatically selected. Fig. 5 (left column) shows the changes in blood concentration and body temperature when the dosage is 200 mg, body weight is 60 kg, and body temperature at the time of administration is 38 °C. It also shows that increasing the dosage to 400 mg causes changes in blood concentration and body temperature (Fig. 5 right column). The pharmacokinetic time-course changes for 200 mg and 400 mg doses, calculated using the Runge-Kutta method with model I, were within the 5th to 95th percentiles of the estimated values for model I (Population B or C) in Fig. 2 and PBPK simulation in Fig. 6 (data not shown). This estimation indicates that while increasing the dosage from 200 mg to 400 mg approximately doubles the blood

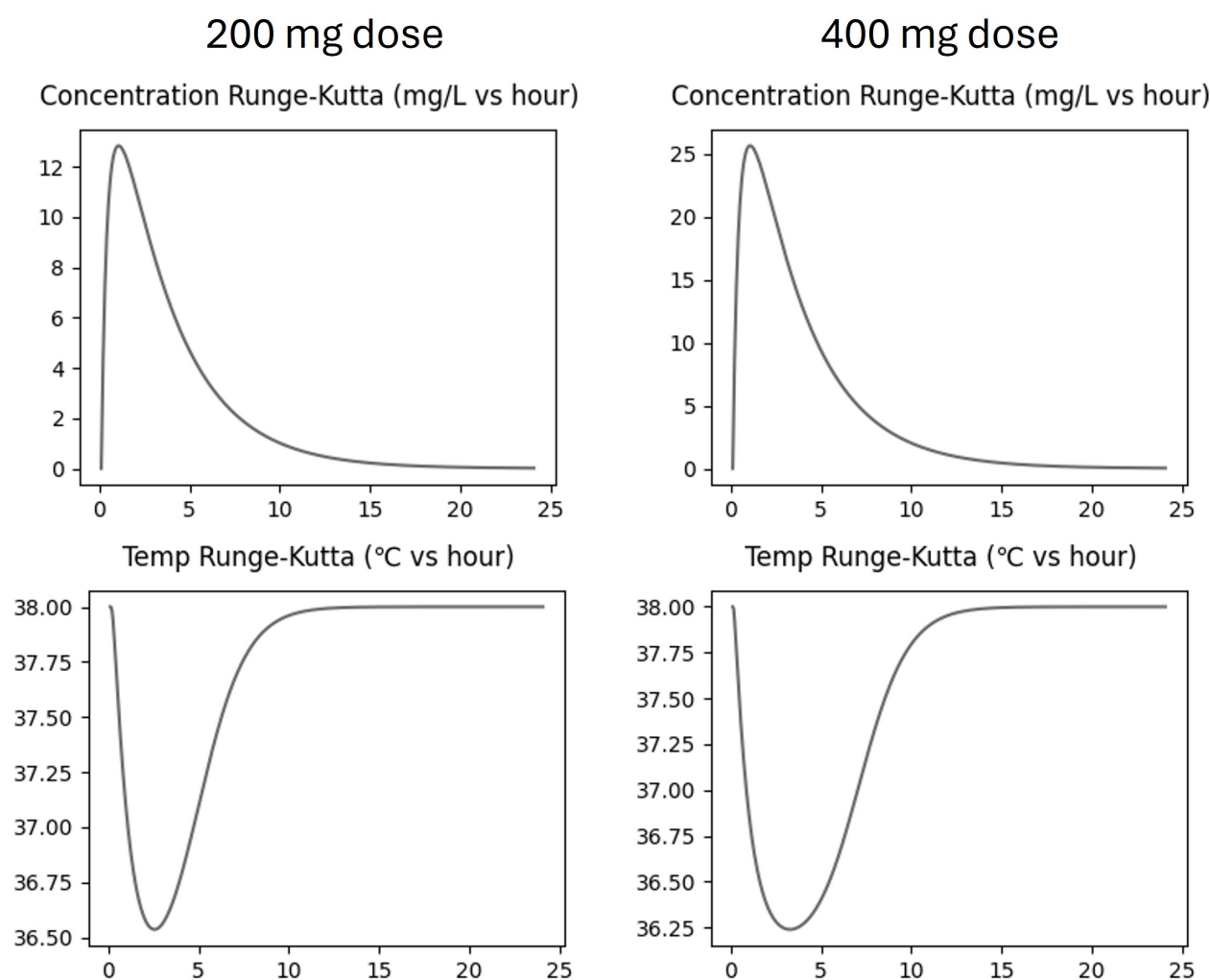


Fig. 5. Visualization of the concentration (mg/L) and body temperature estimation using pharmacokinetic model I. Left and right columns show the VisiblePharm estimation results for ibuprofen doses of 200 mg and 400 mg, respectively, for a patient with a weight of 60 kg, gender of male and initial body temperature of 38 °C.

concentration, there would be no significant clinical difference in antipyretic effect. Although this is just one example, visualizing when and how much a drug is effective in this way is believed to be helpful in supporting a user's understanding of the drug. Therefore, it offers clear impact and information on different dosing regimens or user demographic characteristics.

3.5 Comparison of Estimated Pharmacokinetic Parameters Between Populations

The visualization of ibuprofen's effects on the body using VisiblePharm accurately reproduced the population PK/PD estimation. Another method for estimating the effects of medication on the body is PBPK analysis, which is a mathematical model using parameters such as blood flow and tissue volume in biological tissues. It is commonly used to analyze differences in the pharmacokinetics of populations. The PBPK analysis of ibuprofen pharmacokinetics

across racial groups has revealed that blood concentrations are slightly higher in Asians (Table 4).

In the Simcyp simulator, the body size distribution for Asians is slightly smaller compared with that of other populations, and body weight and height are included as covariates in the estimation formula for model I. Furthermore, a comparison of the pharmacokinetic estimation results in VisiblePharm for a 60 kg body weight and a single 200 mg oral administration of ibuprofen with a PBPK simulation under similar conditions, it appears that VisiblePharm's pharmacokinetic estimation accurately reflects the estimation from PBPK analysis (Fig. 6). The PBPK simulation for the 200 mg ibuprofen dose utilized a Japanese population model, with an age range of 35–55 years, a mean body weight of approximately 60 kg, and a 1:1 male-to-female ratio. Regarding the pharmacokinetics following a single oral dose of 200 mg of ibuprofen (assuming an average body weight of 60 kg), the estimates generated by

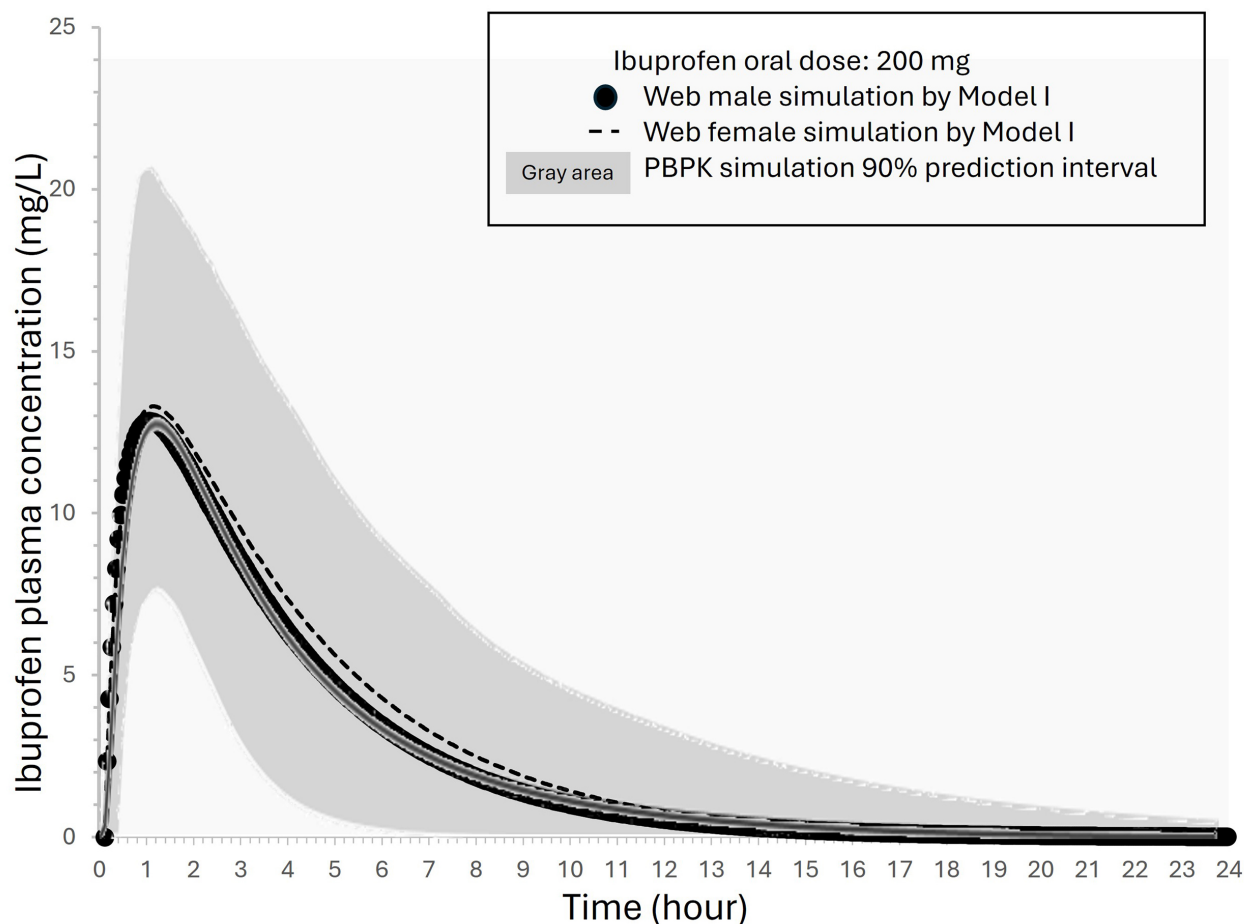


Fig. 6. Visualization of the concentration (mg/L) simulated using model I and comparison with a PBPK simulation. Closed circles indicated the estimation results of VisiblePharm for an ibuprofen dose of 200 mg and a male patient 60 kg in weight, 1.65 m in height, and an initial body temperature of 38 °C. The dotted line indicates the estimation for a female. The gray area indicates the 90% prediction interval for an ibuprofen dose of 200 mg obtained from a PBPK simulation using the Simcyp® Simulator (10 trials with 10 subjects in each trial) in the general Japanese population, for which the average weight for those aged 35–55 years is 60 kg, and assuming a male-to-female ratio of 1:1. The solid gray line indicates the 50th percentile of the PBPK simulation. PBPK, physiologically based pharmacokinetic.

Table 4. Comparison of estimated pharmacokinetic parameters between populations after a single oral administration of ibuprofen 400 mg.

Populations	Cmax (mg/L)	Tmax (h)	AUC (mg/L·h)	CL (L/h)
Healthy North European Caucasian	24.75	1.38	92.74	5.32
General North European Caucasian	24.46	1.39	93.96	5.30
General Japanese	31.03	1.49	129.42	3.71
General Chinese	29.98	1.45	121.24	4.36
Healthy Chinese	28.35	1.50	122.15	4.36
Healthy North American African-American	23.52	1.32	85.68	6.07
Healthy North American White	24.08	1.33	87.22	5.79
Healthy North American Hispanic_Latino	24.62	1.36	93.19	5.49
Healthy North American Asian	26.15	1.34	93.21	5.33

Populations, Simcyp simulator population files (In Simcyp, a ‘general’ is listed as “It is a ‘general’ rather than purely ‘healthy’ population because it is difficult to define a healthy population, and surveys do not usually separate healthy individuals from those with minor health issues and those with major health issues/diseases.”); Cmax, Maximal concentration; Tmax, Time to maximal concentration; AUC, Area under the plasma concentration curve; CL, Clearance.

VisiblePharm fell within the 90% prediction interval of the PBPK analysis, regardless of gender. However, neither the VisiblePharm estimates nor the current PBPK analysis took into account individual factors such as hepatic or renal impairment.

4. Discussion

Ibuprofen is a nonselective inhibitor of prostaglandin synthesis mediated by the cyclooxygenase (COX)-1 and COX-2 enzymes. Inhibiting COX-1 occasionally causes GI side effects in some patients [8]. Ibuprofen is rapidly absorbed into the body; the T_{max} and half-life are about 1.9 and 2.2 h, respectively [20], and hence ibuprofen commonly requires frequent doses [8]. Ibuprofen, like other NSAIDs, is suitable for treating pain or fever if used at the lowest effective dose for the shortest duration. Recently, regulators have warned that there may be serious risks to ibuprofen use even though it is an OTC medicine. NSAID treatment should be stopped once symptoms subside and should not be used for more than three days for fever and five days for pain [8]. The long-term misuse of ibuprofen without medical advice could raise the risk of AEs, such as ulcer complications [2]. Patients commonly expect rapid pain relief after taking ibuprofen, and if this effect is not achieved, they will take an additional dose, believing it will speed the onset of pain relief [3]. In addition, younger and healthier people are typical users of OTC ibuprofen, which may increase their risk because there is no monitoring from clinicians if improper use occurs [2].

The VisiblePharm web application is a tool designed to support safe self-medication. It helps people understand how much of the drug will remain in their bodies through a visualization in simple graph form of the absorbed drug's profile. Thus, the efficacy of the drug can also be estimated and a user can decide whether the drug will be effective based on their specific characteristics (e.g., body weight, height).

We verified the validity of the pharmacokinetic models using the parameter data from previously published population PK models, selected the most appropriate model among them and constructed the web application using the appropriate model. The model comparison showed that model I outperforms model II. An RMSE closer to 0 indicates better prediction accuracy [21,22]. Although the RMSE for the estimates based on model II was slightly lower than that for model I, the VPC and correlation coefficients suggested that model I demonstrated a better goodness-of-fit across multiple population trials regarding pharmacokinetic estimation following ibuprofen administration. Model I included covariates such as body weight, height, and gender in the population pharmacokinetic profile. It was then applied to previously reported fever [9] and dental-pain relief [11] population PD models to identify whether specific characteristics influenced the clinical impact. Various doses (100 mg, 200 mg and 400 mg) were

included in the PK simulation. The PK simulation results reveal that all doses had a linear relationship to blood concentration. An increase in ibuprofen dose is proportional to increases in the drug concentration in blood plasma. This linearity is crucial for predicting drug levels in the body and ensuring the proper dose to avoid toxicity [23]. Evaluation of the maximal concentration and time to reach the therapeutic level are related to severity and recovery time, respectively [12]. In this study, regarding the validation of the PD model, although good predictive capability was demonstrated for the antipyretic effect, the possibility that the estimation results for the analgesic effect included false positives could not be ruled out.

Regarding the PK estimation of ibuprofen, both models I and II demonstrated adequate goodness-of-fit. However, as mentioned above, VPC analysis revealed that model I offered superior estimation validity than model II. Consequently, a web application named "VisiblePharm" was developed to simulate plasma ibuprofen concentrations based on model I using a differential decomposition method. The simulations using model I based on simple demographic data (dose, body weight, height, gender, and initial status) indicated that the model could achieve estimation accuracy comparable to current nonlinear analysis methods. While the scope for personalization is limited to variations dependent on body size, the application demonstrated the potential to easily able to visualize changes in blood concentration and body temperature following ibuprofen administration. We believe this study could serve as a first step toward developing other self-medication supporting tools as well.

5. Limitations

One limitation of this study is the use of published data for PK data modelling. To finalize the population pharmacokinetics model for ibuprofen and ensure its validity, it will be necessary to verify its correlation with clinical data.

This PK model targets adults. Although the pediatric data regarding antipyretic effects demonstrated a certain level of validity, recommending self-medication for children requires rigorous verification; this is because the risk factors and sources of variability are more complex in pediatric populations, and numerous aspects of self-treatment must be considered.

This study serves as a proof-of-concept for the visualization of the physiological effects of drug administration. While the study demonstrated that the pharmacokinetics and antipyretic effects of ibuprofen can be readily visualized, the results were estimated based on specific individual factors used as covariates; therefore, increasing estimation accuracy will require considering multiple individual factors, such as renal and hepatic function.

6. Conclusions

In this study, we developed a web application that facilitates the visualization of a drug's effects on the body by utilizing previously reported, significant pharmacokinetic findings that would otherwise be difficult to communicate in a practical clinical setting. Although the estimation accuracy requires further validation, the results suggest that this application could enable the general public to easily visualize changes in plasma ibuprofen concentrations and understand the impact of ibuprofen on therapeutic efficacy. Further validation against clinical data could enable this type of application to contribute to a better understanding of the appropriate use of OTC drugs in self-medication and help prevent unexpected AEs.

Availability of Data and Materials

The datasets and model descriptions analyzed in this study are available from the corresponding author upon reasonable request.

Author Contributions

SAP and KO contributed equally to this work. SAP and KO conceived, designed, conducted this research and experimental sessions, participated in the research process and data analysis and shared responsibility for drafting the manuscript and refining it. KI verified the validity of the study at each stage—conception, design, implementation, and data analysis—supervised and confirmed the validity, revisions of the manuscript and was responsible for designing the graphical abstract. All authors contributed to editorial changes in the manuscript, read, approved the final manuscript, have participated sufficiently in the work, agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/Pharmazie55064>.

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