

# Population pharmacokinetics of intravenous acetaminophen in Japanese patients undergoing elective surgery

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## Abstract

**Introduction** Intravenous (i.v.) acetaminophen is administered during surgery for postoperative analgesia. However, little information is available on the pharmacokinetics of i.v. acetaminophen in Japanese patients undergoing surgery under general anesthesia.

**Methods** The study was approved by the Institutional Review Board and registered at UMIN-CTR (UMIN000013418). Patients scheduled to undergo elective surgery under general anesthesia were enrolled after obtaining written informed consent. During surgery, 1 g of i.v. acetaminophen was administered over 15, 60, or 120 min. Acetaminophen concentrations (15 or 16 samples per case) were measured at time points from 0–480 min after the start of administration (liquid chromatography–mass spectrometry/tandem mass spectrometry; limit of quantitation 0.1 µg/mL). The predictive performance of three published pharmacokinetic models was evaluated. Population pharmacokinetics were also analyzed using a nonlinear mixed-effect model based on the NONMEM program.

**Results** Data from 12 patients who underwent endoscopic or lower limb procedures were analyzed (male/female = 7/5, median age 55 years, weight 63 kg).

Anesthesia was maintained with remifentanyl and propofol or sevoflurane. The pharmacokinetic model of i.v. acetaminophen reported by Würthwein et al. worked well. Using 185 datapoints, the pharmacokinetics of i.v. acetaminophen were described by a two-compartment model with weight as a covariate but not age, sex, or creatinine clearance. The median prediction error and median absolute prediction error of the final model were –1 and 10%, respectively.

**Conclusion** A population pharmacokinetic model of i.v. acetaminophen in Japanese patients was constructed, with performance within acceptable ranges.

**Keywords** Intravenous acetaminophen · Population · Pharmacokinetics

## Introduction

Acetaminophen is commonly used as a postoperative analgesic for patients who undergo surgery. According to the manufacturer's information accompanying the intravenous (i.v.) acetaminophen (Acelio<sup>®</sup>; Terumo Corp., Japan), the maximal dose for adults is 1 g of Acelio<sup>®</sup>, and for patients with body weight <50 kg, the maximal dose should be 15 mg/kg. However, because the mean weights of adult Japanese men and women are 65.8 ± 11 and 53.2 ± 9.3 kg, respectively, based on Japanese government statistics for 2014 [1], many Japanese patients should receive the uniform dose of 1 g.

In general, the amount of anesthetics administered in single dose is calculated on the basis of body size scalars, such as weight, in accordance with the pharmacokinetic (PK) characteristics of the drug. When designing a dosing regimen for i.v. acetaminophen, it is reasonable to base this on a body size scalar to avoid potential underdosing or

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overdosing and to use computer simulation of plasma or effect site drug concentrations with appropriate PK models of acetaminophen so that drug concentrations will achieve the therapeutic range.

For this purpose, PK models with compartmental model structures are required because usual PK simulation programs used mainly by anesthesiologists, such as Tivatrainner<sup>®</sup> (<http://www.eurosiva.eu/tivatrainner/TTweb/TTinfo.html>; last accessed on July 22, 2016) or STAN-PUMP (<http://opentci.org/code/stanpump>; last accessed on July 22, 2016), predict the time course of plasma drug concentrations using compartmental PK parameter estimates (such as for the volume of distribution, clearance, or rate constant), rather than the results of non-compartmental analysis. As yet, there have been no reports of a compartmental PK model for i.v. acetaminophen in Japanese adults. In non-Japanese patients, some PK models of i.v. acetaminophen for adolescent [2] or adult [3, 4] perioperative patients have been reported, with various factors that influence PK parameter estimates, including age [3, 4], creatinine clearance [3], and body size [4]. Although the results of non-compartmental PK analysis suggest that acetaminophen administration is not prone to intrinsic ethnic differences between Japanese and non-Japanese [5], whether the PK models with compartmental structures mentioned above also predict the correct plasma drug concentrations in Japanese patients is still unknown.

The aim of this study was therefore to evaluate the predictive performances of three published PK models [2, 3, 6] for i.v. acetaminophen and to build a compartmental population PK model for i.v. acetaminophen in Japanese patients who undergo surgery under general anesthesia.

## Methods

This study was approved by Fukushima Medical University Ethics committee (approval number: 1941) and was registered at UMIN-CTR (UMIN0000 13418). The study design was a single-dose PK study using multiple study groups and sampling intervals and a population PK study.

Twelve patients aged 18–75 years who were scheduled to undergo elective surgery and who would receive i.v. acetaminophen for postoperative analgesia were enrolled. Their physical status was American Society of

Anesthesiologists classification I–II. All patients provided written informed consent. Exclusion criteria included a known allergy to acetaminophen; psychoneurotic disorders; psychiatric pharmacotherapy; chronic use of acetaminophen, NSAIDs or opioids; women who were pregnant or breast-feeding; anemia (hemoglobin <8 g/dL); liver or advanced renal dysfunction; and those who were considered inadequate. The patients were randomly allocated to three groups according to the duration of acetaminophen infusion—(1) the ‘short’ group (1 g of acetaminophen infused over 15 min), (2) the ‘medium’ group (1 g of acetaminophen infused over 60 min), and (3) the ‘long’ group (1 g of acetaminophen infused over 120 min). This allocation was intended to facilitate the observation of the time course of plasma acetaminophen concentrations at different infusion speeds. The patients did not receive premedication. In the operating room, standard monitoring was performed, including electrocardiography, noninvasive blood pressure monitoring, pulse oximetry, capnometry, and body temperature measurements. General anesthesia was induced and maintained at the attending anesthesiologist’s discretion. During surgery, 1 g of i.v. acetaminophen was infused over the selected duration (15, 60, or 120 min) using two infusion pumps (TE-SS702 N<sup>®</sup>; Terumo Corp., Japan). Venous blood samples (5 mL) were collected from each patient up to 8 h after the initiation of infusion of i.v. acetaminophen (detailed in Table 1).

Blood samples were collected into heparinized tubes and immediately placed on ice, with the plasma separated by centrifugation at 3000g for 10 min. Plasma samples were stored at –70 °C until analysis. Human plasma concentrations of acetaminophen were measured using liquid chromatography–tandem mass spectrometry, performed using a Prominence UFLC (Shimadzu Corporation KK, Japan) and an API5000 (AB/MDS Sciex, USA). Verapamil hydrochloride was used as an internal standard. Chromatographic separation was performed on a 2.1 mm × 75 mm, 2.7 μm Ascentis Express C18 column (Sigma-Aldrich Co. LCC, Japan) according to the following gradient method (where A is 0.1% formic acid solution and B is acetonitrile)—0.00–2.00 min, 95:5–40:60 A:B v/v; 2.01–4.00 min, 40:60 A:B v/v; 4.00–4.01 min, 40:60–95:5 A:B v/v; and 4.01–6.50 min, 95:5 A:B v/v. The chromatographic analysis time was 6.5 min per sample. Calibration curves in human plasma were linear between 0.1 and 50 μg/mL with  $1/x^2$  as

**Table 1** Sampling schedule for measuring acetaminophen concentrations for each treatment group

Group	Sampling schedule
‘Short’ group	0, 1, 2, 4, 8, 12, 15, 17, 20, 25, 30, 60, 120, 240, 360, and 480 min after beginning dosing
‘Medium’ group	0, 5, 10, 15, 25, 35, 60, 65, 75, 80, 90, 120, 240, 360, and 480 min after beginning dosing
‘Long’ group	0, 5, 15, 25, 35, 60, 90, 120, 125, 130, 140, 150, 180, 240, 360, and 480 min after beginning dosing

a weighting factor ( $r \geq 0.99$ ). The limit of quantitation was  $0.1 \mu\text{g/mL}$ . The limit of detection was  $0.013 \mu\text{g/mL}$ .

**Evaluation of existing PK models**

Using the infusion history of acetaminophen and measured plasma acetaminophen concentrations obtained in the present study as an evaluation dataset, the predictive performances of the three published PK models (detailed in Table 2) were evaluated by calculating median absolute prediction error (MDAPE) as a measure of accuracy and median prediction error (MDPE) as a measure of bias, as previously described by Varvel et al. [7] to compare prediction ability between the models.

**PK modeling**

Population compartmental PK parameters were estimated using a mixed-effects population approach based on the NONMEM program (version 7.2, ICON Development Solutions, Ellicott City, MD, USA). Inter-individual

errors for each parameter were modeled using a log-normal error model. Residual intra-individual errors were modeled using an additive and proportional variance model. The first-order conditional estimation method was used for all estimates. Covariates were evaluated, including age, sex, height, weight, and creatinine clearance. Continuous covariates other than weight were centered at their median value and tested for inclusion using a linear relationship. Categorical covariates were tested for inclusion using indicator variables. Covariates were selected based on a ‘forward selection’ and then a ‘backward elimination’ approach. A respective decrease or increase in the objective function value  $>6.63$  ( $P < 0.01$ ) or  $10.83$  ( $P < 0.001$ ) for the inclusion or elimination of covariates was considered to be statistically significant.

When evaluating the effect of weight as a covariate for each PK parameter, all parameter values were standardized to a median value using an allometric model [8] as follows:

$$P_{\text{individual}} = P_{\text{typical}} \times (\text{WT}_{\text{individual}}/\text{median weight})^{\text{PWR}}$$

**Table 2** Pharmacokinetic parameter estimates and study backgrounds of the validated models

	Würthwein et al. [2]	Wang et al. [6]	Owens et al. [3]	
Population parameters			Population parameters	
V1 (L)	13.2* (WT/70)	25.1* (WT/70)	V <sub>c</sub> (L)	13.9
V2 (L)	33* (WT/70)	36.1* (WT/70)	V <sub>T</sub> (L)	50.9
V3 (L)		21.6* (WT/70)	V <sub>G</sub> (L)	102
CL1 (L/min)	(13.2/60)* (WT/70) <sup>0.75</sup>	0.293* (WT/70) <sup>k</sup>	V <sub>S</sub> (L)	5.72
CL2 (L/min)	(45.7/60)* (WT/70) <sup>0.75</sup>	1.613* (WT/70)	V <sub>O</sub> (L)	17.9
CL3 (L/min)		0.023 * (WT/70)	Q (L/h)	77.5
k		$k_0 - k_{\text{max}} \text{WT}^\gamma (k_{50}^\gamma + \text{WT}^\gamma)$	CL <sub>PG</sub> (L/h)	$8.92 * (\text{age}/\text{median age})^{-0.00152}$
k <sub>max</sub>		0.45	CL <sub>PS</sub> (L/h)	0.903
k <sub>0</sub> - k <sub>max</sub>		0.75	CL <sub>PO</sub> (L/h)	0.533
k50		12.2	CL <sub>RG</sub> (L/h)	$3.81 * (\text{CrCL}/\text{median CrCL})^{-0.0129}$
γ		1.4	CL <sub>RS</sub> (L/h)	3.13
			CL <sub>RO</sub> (L/h)	3.51
			CL <sub>RP</sub> (L/h)	0.137
Population	Children and adolescents	Preterm and term neonates, infants, children and adults	Adults	
No. of subjects	7	220	53	
No. of sample	37	Not applicable	Not applicable	
WT range (kg)	39.3–80.0	0.5–94	54–129	

V1 and Vc volume of distribution of the central compartment, WT body weight, V2 V3 and V<sub>T</sub> volume of distribution of the peripheral compartment, V<sub>G</sub> volume of distribution of acetaminophen glucuronide, CL1 central compartment clearance, V<sub>S</sub> volume of distribution of acetaminophen sulfate, CL2 and CL3 peripheral compartment clearances, V<sub>O</sub> volume of distribution of acetaminophen cysteine + mercapturate, Q intercompartmental clearance, k bodyweight-dependent exponent, k<sub>0</sub> value of k at a theoretical bodyweight of 0 kg, k<sub>max</sub> maximum decrease of k, γ the Hill coefficient that determines the steepness of the sigmoidal decline in k, k<sub>50</sub> the bodyweight at which a 50% decrease in the maximum decrease of k is attained, CL<sub>PG</sub> formation clearance of acetaminophen glucuronide, CL<sub>PS</sub> formation clearance of acetaminophen sulfate, CL<sub>PO</sub> formation clearance of acetaminophen cysteine + mercapturate, CL<sub>RG</sub> renal clearance of acetaminophen glucuronide, CrCL creatinine clearance (ml/min), CL<sub>RS</sub> renal clearance of acetaminophen sulfate, CL<sub>RO</sub> renal clearance of acetaminophen cysteine + mercapturate, CL<sub>RP</sub> renal clearance of unchanged/parent acetaminophen

where  $P_{\text{individual}}$  is the parameter of the individual,  $WT_{\text{individual}}$  is the weight of the individual, and  $P_{\text{typical}}$  is the parameter for an individual with the median weight, which in the present study was 70 kg. The PWR exponent was set at 0.75 for clearance parameters and 1 for distribution volumes. The quality of the various population models constructed by NONMEM was assessed in terms of their ability to predict measured plasma concentrations using MDAPE and MDPE. The models were also visually assessed by plotting measured/predicted concentrations versus time, and the final model was selected. A bootstrapping technique with 1000 replications by PLT tools free version 5.4.0 (<http://www.pltsoft.com/>; last accessed on February 16, 2017) was used to compute 95% confidence intervals (CIs) for each parameter in the final model for the internal validation of the model and to evaluate parameter uncertainty. Computer simulations using the covariate-adjusted population PK model (i.e., the final model) were conducted to evaluate the influence of covariates on the transition of plasma acetaminophen concentrations with NONMEM program. First, we explored the time course of plasma acetaminophen concentration when 1 g of i.v. acetaminophen is administered to subjects with various body weights (50, 67, and 85 kg) over 15 min. The same simulations were performed using three existing PK models [2, 3, 6] (Table 2) with two- or three-compartment model structures. Next, the time courses of plasma acetaminophen concentration following three different infusion durations (15, 60, and 120 min) were simulated using the PK model constructed in the present study.

R version 3.2.0 (the R foundation for Statistical Computing) was used for statistical analyses and graph generation.

## Results

### Patients and surgical procedures

The details of the 12 patients (7 male/5 female) included in this PK study are presented in Table 3. The median age was 55 years (range 38–74 years), the median height was 163 cm (range 153.4–171.0 cm), and median weight was 63 kg (range 50.0–85.3 kg). The final two samples could not be collected for one patient in the ‘short’ group (patient ID 10) because of occlusion of the sampling port. In total, 185 data points (Fig. 1) were obtained. Data points were ignored if the acetaminophen concentrations after the start of infusion were below the limit of quantitation; this was the case for three data points, all at 1 min after the start of acetaminophen infusion in the ‘short’ group. General anesthesia was induced with propofol, remifentanyl, and rocuronium and maintained with propofol or sevoflurane and remifentanyl, with or without fentanyl.

### External evaluation

As illustrated in Fig. 2, the MDPE and MDAPE for the PK model reported by Würthwein et al. were within the acceptable range (panel A), where MDPE is between –20 and 20% and MDAPE is <30% [9]. In contrast, the MDPE and MDAPE for the PK model reported by Wang et al. and Owens et al. were out of the acceptable range (panel B and C).

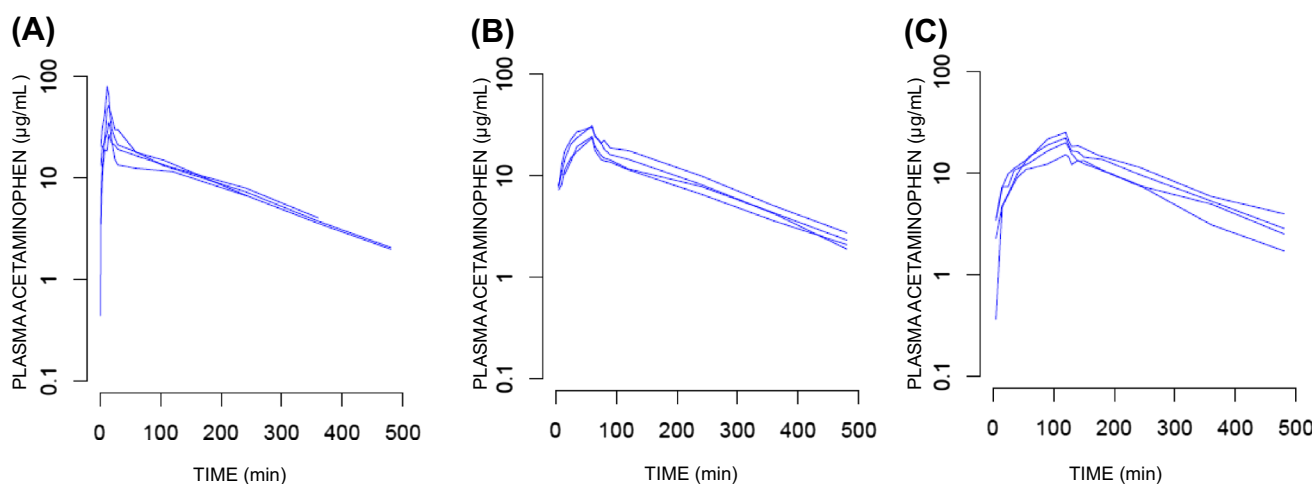
### Pharmacokinetic analysis

The PKs of i.v. acetaminophen were best described using a two-compartment model with weight as a covariate

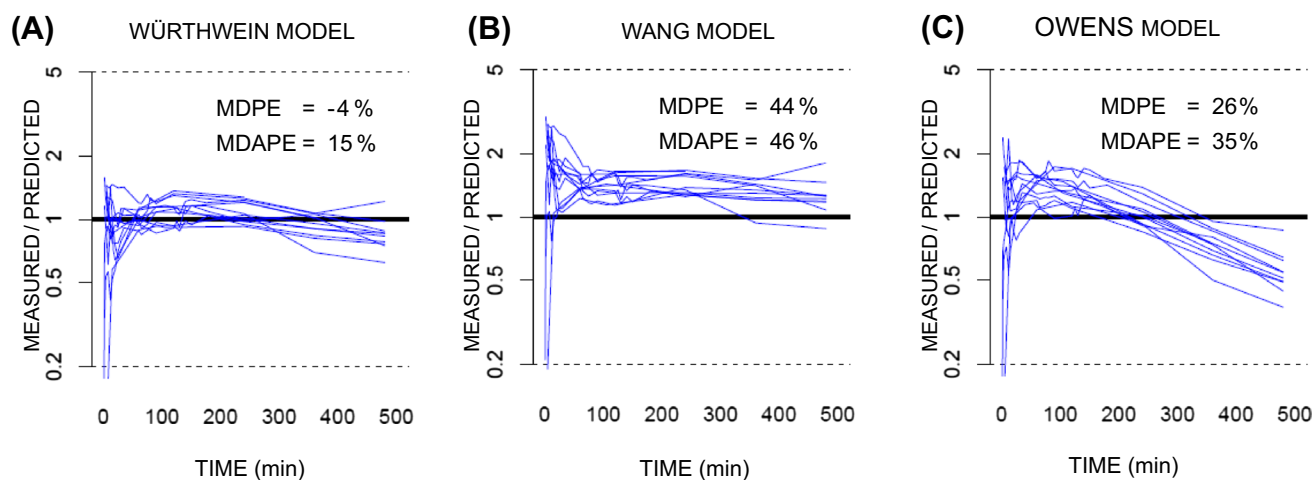
**Table 3** Patient backgrounds and clinical data from the pharmacokinetics study

ID	Sex	ASA	Age (year)	Height (cm)	Weight (kg)	CrCL	Group	Surgical procedures
1	F	1	40	163	70	112	Long	Laparoscopic myomectomy
2	M	2	74	170.5	55.2	65	Long	Laparoscopic prostatectomy
3	F	2	46	161.7	75.4	123	Long	Laparoscopic cholecystectomy
4	M	2	68	159.6	50.5	57	Long	Laparoscopic prostatectomy
5	M	1	41	166.3	73.7	102	Medium	Removal of tumor in lower limb
6	F	1	40	171	57	140	Medium	Laparoscopic ovary removal
7	F	2	38	165.2	69.4	152	Medium	Laparoscopic myomectomy
8	M	2	63	163.4	61.5	64	Medium	Laparoscopic prostatectomy
9	M	2	67	157	50	60	Short	Laparoscopic cholecystectomy
10	M	2	71	166.5	85.3	66	Short	Laparoscopic cholecystectomy
11	F	2	42	153.4	57	96	Short	Removal of tumor in lower limb
12	M	2	70	159.9	63.4	66	Short	Laparoscopic prostatectomy

ASA American Society of Anesthetists classification, CrCL creatinine clearance (ml/min)



**Fig. 1** Acetaminophen concentration versus time on a log scale after 1 g of acetaminophen was administered intravenously over 15 min (**a**  $n = 4$ ), 60 min (**b**  $n = 4$ ), or 120 min (**c**  $n = 4$ )



**Fig. 2** Measured/predicted values versus time in three different existing pharmacokinetic models reported by Würthwein et al. [2] (**a**), Wang et al. [6] (**b**), and Owens et al. [3]. *MDPE* median performance error, *MDAPE* median absolute performance error

(Table 4). The PK model parameter estimates of simple (i.e., no covariate effects) and final (significant covariate effects) models are detailed in Table 4. The weight-scaled model demonstrated better performance than the simple model. After incorporating this covariate effect, the objective function significantly improved from 369.3 to 355.7. Age, sex, and creatinine clearance were not included as significant covariates in the final model. The plots of measured versus predicted value and measured divided by predicted value against time (*M/P* plots) are illustrated in Fig. 3. The data points were distributed around the line of identity (Fig. 3a, b). In one of the ‘long’ group patients, the *M/P* value was  $0.37/3.7 = 0.1$  at 5 min after acetaminophen infusion (patient ID 4); however, in another patient in the ‘short’ group (patient ID 10), the *M/P* value

was  $0.44/4.4 = 0.1$  at 1 min after acetaminophen infusion, showing extremely low *M/P* values (below the lower limit of the vertical axis in Fig. 3b). The *MDPE* and *MDAPE* of the final model were  $-1$  and  $10\%$ , respectively. The predictive performance of the final model was within the acceptable range. The median values of the PK parameter estimates and the inter- or intra-variability obtained from the 1000 bootstrapping resampling were comparable to those of the final model (Table 4).

### Simulations

PK simulations using the current and existing models for patients with three different body weights (50, 67, and 85 kg) who received 1 g of i.v. acetaminophen

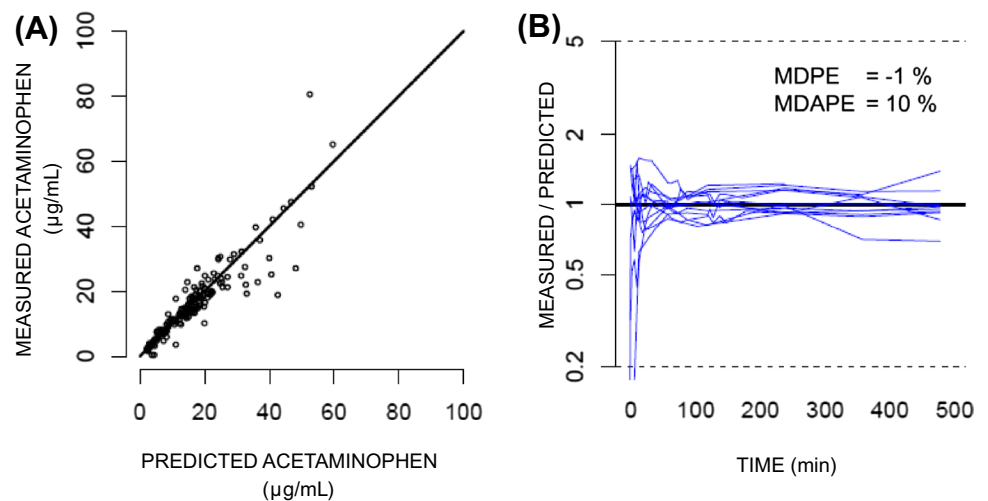
**Table 4** Pharmacokinetic parameters and performance of the current model

	Simple model	Simple model	
Population parameters	Estimates	Estimates	Bootstrap median (95% CI)
V1 (L)	10.5	= TVV1 × (WT/70)	
TVV1		11.8	11.7 (8.9–15.3)
V2 (L)	27.1	= TVV2 × (WT/70)	
TVV2		29.8	29.6 (26.5–33.5)
CL1 (L/min)	0.21	= TVCL1 × (WT/70) <sup>0.75</sup>	
TVCL1		0.22	0.22 (0.21–0.24)
CL2 (L/min)	1.1	= TVCL2 × (WT/70) <sup>0.75</sup>	
TVCL2		1.21	1.20 (0.97–1.41)
Inter-individual variability (%)			
ωV1	45.6	40.8	42.5 (18.4–59.9)
ωV2	21	16.3	16.4 (7.7–28.0)
ωCL1	12	8	8.0 (4.0–10.6)
ωCL2	23.7	24.5	24.4 (3.5–42.6)
Intra-individual variability			
Additive (μg/ml)	0.44	0.45	0.41 (0–1.11)
Proportional (%)	9.1	8.9	8.7 (4.4–11.1)
Model performances			
MDPE (%)	0	–1	
MDAPE (%)	15	10	
Objective function	369.3	355.7	

95% confidence intervals (CI) from 1000 bootstrap replicates were calculated based on the 2.5 percentile and 97.5 percentile. Convergence was successful for 954 of the 1000 bootstrap data sets

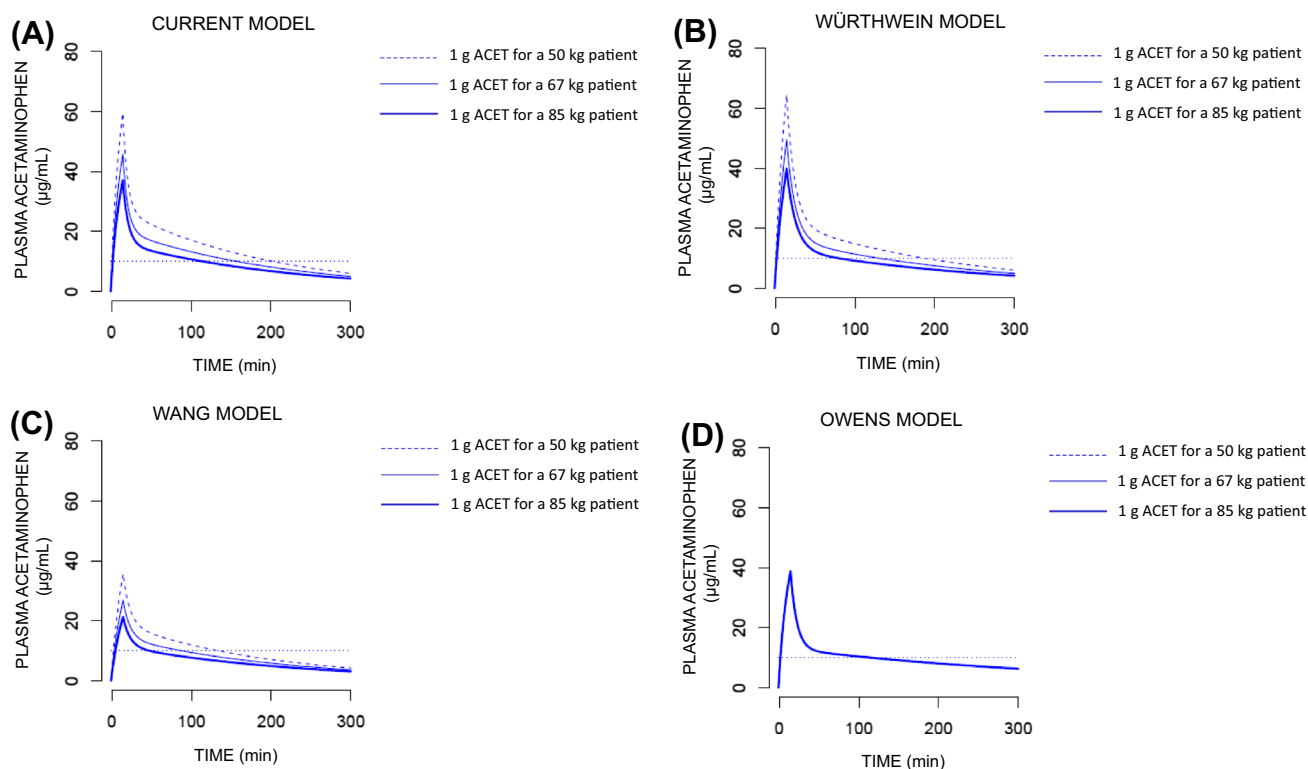
*V1* distribution volume of the central compartment, *TVV1* typical value of the distribution volume of the central compartment, *WT* weight, *V2* distribution volume of the peripheral compartment, *TVV2* typical value of the distribution volume of the peripheral compartment, *CL1* central compartment clearance, *TVCL1* typical value of central compartment clearance, *CL2* peripheral compartment clearance, *TVCL2* typical value of peripheral compartment clearance, *ω* square root of variance of inter-individual variability, *MDPE* median prediction error, *MDAPE* median absolute prediction error

**Fig. 3** Measured versus predicted acetaminophen concentrations (a) and measured/predicted values versus time (b) in the final pharmacokinetic model. The black bold lines represent the line of identity. *MDPE* median performance error, *MDAPE* median absolute performance error



administered over 15 min are shown in Figs. 4a–d. In the current model, the predicted peak concentrations differed for all three body weights (59.5, 45.9,

and 37.1 μg/mL). The earliest decline in plasma acetaminophen concentration below the lower limit of the therapeutic range (assuming this to be 10 μg/mL [10])

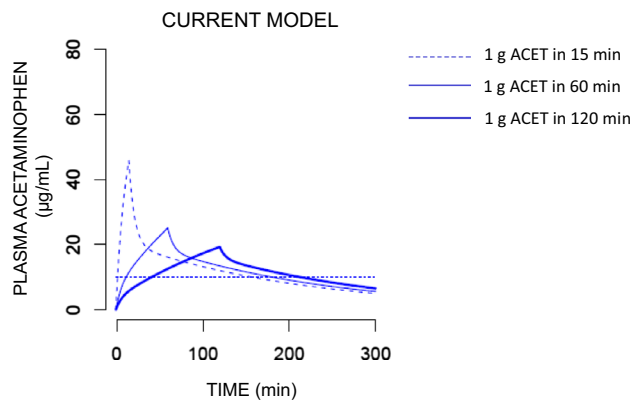


**Fig. 4** Simulations of 1 g of intravenous acetaminophen administered to patients with different body weights using the current model (a) and previous models reported by Würthwein et al. [2] (b),

Wang et al. [6] (c), and Owens et al. [3] (d). Horizontal dot lines are assumed to be the lower limit of the therapeutic range (10 µg/mL [10])

was seen in the heaviest patient, with this decline taking 204 min, 158 min, and 116 min after the start of acetaminophen infusion in patients weighing 50, 67, and 85 kg, respectively (Fig. 4a). Simulations using the PK model reported by Würthwein et al. simulated similar time courses of plasma acetaminophen concentrations to those predicted by the current PK model (Fig. 4b). The PK model reported by Wang et al. predicted largely different peak plasma acetaminophen concentrations; however, these were lower than those predicted by the other two PK models (Fig. 4c). The PK model reported by Owens et al. predicted identical concentration time courses for acetaminophen among patients with different body weights (Fig. 4d) because the PK model parameters are not influenced by body weight as seen in Table 2.

The time courses in the current PK model for plasma acetaminophen concentration after the administration of 1 g of i.v. acetaminophen to a patient weighing 67 kg over three different durations (15, 60, and 120 min) are depicted in Fig. 5. The maximum plasma acetaminophen concentrations reached were 45.9, 25.2, and 19.3 µg/mL, respectively, and the concentrations declined <10 µg/mL at 158, 182, and 214 min after the start of acetaminophen infusion.



**Fig. 5** Simulations of 1 g of intravenous acetaminophen (ACET) administered to patients (weight 67 kg) over different durations using the current model. The horizontal dotted line indicates the assumed lower limit of the therapeutic range (10 µg/mL [10])

## Discussion

The novelty of the present study is that the predictive performances of three published PK models were evaluated in Japanese patients who underwent surgery and received i.v. acetaminophen over durations identical to or longer

than that recommended, and that a compartmental population PK model of i.v. acetaminophen was constructed showing clinically acceptable prediction performance.

In our dataset, two data points (for two patients) were observed with M/P values that were extremely low, both relating to the first blood sample after administration. One assumption of this type of compartmental model is that the drug administered to the central compartment is instantaneously mixed. However, this generally accepted assumption in pharmacology is not matched by reality and makes it difficult to predict the plasma drug concentration in the first minutes after administration, as has been reported for propofol [11]. This limitation could have affected the M/P values in our results. However, considering that the prediction performance for acetaminophen concentration is more important in the elimination phase than the initial distribution phase because of the relatively long-acting nature of analgesics, the two low M/P values in our results can be clinically overlooked.

Three published PK models were evaluated using our acetaminophen dosing and concentration records. The PK model reported by Wang et al. showed an unacceptable model performance. However, the original dataset of their model was not from perioperative patients but from non-Japanese neonates, infants, and children and healthy young adult volunteers, and so it is not unreasonable that it did not precisely predict acetaminophen concentrations for adult Japanese surgical patients. The performance of the model reported by Owens et al. was also unacceptable. Their PK data were obtained from New Zealand or Irish patients who underwent major abdominal or breast surgeries. The potential differences in their study design compared to that of ours are that they performed more invasive procedures, and their PK data included the duration of metabolic conversion to acetaminophen glucuronide and subsequent urinary clearance in 2–3 days after surgery [12]. These differences may have affected poor predictive performance. However, from the above two analyses, it is difficult to determine the exact contribution of ethnic differences on the results due to differences in other elements of the study designs. In contrast, the model reported by Würthwein et al. worked well. Although the original dataset of their model was from non-Japanese children and adolescents, the range of weight was not far from that of our evaluation dataset, which may be the reason for the good prediction performance of their model. Their model did not include age as a covariate, a factor that could have resulted in worse performance when the model was extrapolated to adults. However, the PKs in patients in our evaluation dataset were not influenced by age (i.e., the final model did not include age as a covariate). Due to these similarities, we concluded that ethnical differences did not affect the prediction of the PK model with a compartment structure.

Factors that influence the PKs of i.v. acetaminophen have been reported in different study settings. In studies of perioperative patients, age and sex [13], and age and creatinine clearance [3] were found to affect PK parameters. In a PK analysis using a pooled historical dataset from past PK studies, including not only perioperative patients but also healthy volunteers, intensive care unit patients, and perinatal women, Allegart et al. [4] concluded that size, including an allometrically scaled body weight and normal fat mass (extension of the concept of predicted normal weight), and age were important covariates. In a study of adolescent patients, Würthwein et al. [2] constructed a two-compartment PK model and identified weight as a covariate in all PK parameter estimates (Table 2), which has a structure and parameter estimate values similar to those in the final model constructed in the present study.

Simulations to show the impact of weight on the final model were conducted (Fig. 4a), demonstrating a lower peak and a faster decline in plasma acetaminophen concentration with heavier body weight, which is naturally reasonable. In the non-compartmental PK analysis of i.v. acetaminophen in young and healthy Japanese subjects ( $29.4 \pm 4$  years old and  $66.1 \pm 9$  kg; mean and standard deviation), the peak plasma acetaminophen concentration was  $46.2 \pm 5.9$   $\mu\text{g/mL}$  [5]. Assuming that this acetaminophen concentration is expected for a typical patient, the peak plasma acetaminophen concentration ( $37.1$   $\mu\text{g/mL}$ ) simulated for a heavier patient may be inadequate. In analyzing the drug effects using a compartmental PK model, the transition of the drug from the central compartment to the effect site should be taken into account as the drug concentration would enhance the drug effect. The cerebrospinal fluid (CSF) concentrations can be equated to be the effect site concentrations [14] because the time course of acetaminophen concentration in CSF correlates with the analgesic and antifebrile effect of the drug [15]. Because acetaminophen is thought to penetrate the blood–brain barrier by passive diffusion due to a concentration gradient, larger peak concentrations after i.v. administration would contribute to increased acetaminophen concentrations in CSF. Thus, as stated before, the lower peak concentrations in heavier patients or slow infusion of i.v. acetaminophen may delay the onset; these concerns should be examined in the future. The PK model constructed in this study and the results of simulations have the potential to provide fundamental information regarding the uniform dosing of 1 g acetaminophen to heavy patients and the effect of infusion speed for i.v. acetaminophen.

The present study had some limitations. First, the ranges for age and weight of the study population were not wide. In addition, we could not unify the surgical procedure received by the patients because of the operating schedule at our institution. Notably, most of our patients underwent



laparoscopic surgeries, which can reduce liver blood flow due to the increase in abdominal air pressure. Clearance of anesthetics with a high hepatic extraction like propofol is largely dependent on liver blood [16]. However, because the hepatic extraction ratio of acetaminophen is relatively low (0.11–0.37) [17], we speculate that the effect of receiving laparoscopic surgeries on the metabolism of acetaminophen is restrictive. The extrapolation of the predictions of our PK model to other populations including older or heavier patients or patients scheduled to undergo different types of procedures including more invasive surgery, should be performed with caution. External evaluation to confirm the model predictions for such patients should ideally be performed in future.

In conclusion, the PK model reported by Würthwein et al. worked well when evaluated in Japanese patients who underwent surgery under general anesthesia. A compartmental population PK model was constructed to simulate i.v. acetaminophen concentration. The administration regimen contained slower infusion speeds than recommended. Body weight was identified as a covariate in the final model parameter estimates. PK simulations with the model demonstrated lower peak plasma acetaminophen concentrations in heavier patients and in patients administered a uniform dose of 1 g acetaminophen at a slow infusion speed.

**Author contributions** TI helped conduct the study, analyze the data, and write the manuscript. TI has seen the original data, reviewed the analysis of the data, and approved the final manuscript. SO helped design the study, conduct the study, analyze the data, and write the manuscript. SO has seen the original data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files. MM helped conduct the study, reviewed the analysis of the data and approved the final manuscript. YI helped conduct the study, reviewed the analysis of the data and approved the final manuscript. MH helped conduct the study, reviewed the analysis of the data and approved the final manuscript. MM helped design the study, conduct the study, and write the manuscript; MM also reviewed the analysis of the data and approved the final manuscript.

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#### Compliance with ethical standards

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