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RESEARCH PAPER

A Semi-mechanistic Gastric Emptying Model for the Population Pharmacokinetic Analysis of Orally Administered Acetaminophen in Critically Ill Patients

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ABSTRACT

Purpose To develop a semi-mechanistic population pharmacokinetic model based on gastric emptying function for acetaminophen plasma concentration in critically ill patients tolerant and intolerant to enteral nutrition before and after prokinetic therapy.

Methods Acetaminophen plasma concentrations were available from a study with 10 tolerant and 20 intolerant patients before and after prokinetic therapy with either erythromycin or metoclopramide. Population pharmacokinetic modelling was carried out in a nonlinear mixed effects analysis software, NONMEM.

Results A four-compartment semi-mechanistic model for stomach, intestine, central and peripheral compartments was described. The rate of emptying of the stomach was described by a first-order rate parameter. The final model has two gastric emptying rate constant parameters: kg1 (1.30 h^{-1}, RSE = 53.84%, T1/2 = 0.53 h) for the intolerant group before prokinetic therapy and kg2 (27.8 h^{-1}, RSE = 59.35%, T1/2 = 0.025 h) for both the intolerant group after prokinetic therapy and the tolerant group. Other parameters and estimates (RSE) in the model were ka = 5.12 h^{-1} (28.13%), CL = 13.0 L/h (19.62%), CLD = 22.6 L/h (19.78%), V1 = 63.8 L (12.79%) and V2 = 69 L (38.70%).

Conclusions The four-compartment semi-mechanistic population pharmacokinetic model adequately described the data. The gastric emptying half-time is improved by a factor of about 20 in the patients that are intolerant to enteral nutrition after treatment with prokinetic agents.

KEY WORDS gastric emptying · mixed effects modelling · paracetamol · population pharmacokinetics · prokinetic agents

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INTRODUCTION

Gastric emptying is the rate at which food and drink leave the stomach. Gastric emptying is important for oral absorption of drugs and nutrients from the small intestine, where absorption is more rapid compared to the stomach (1). Abnormal gastric emptying (slow or rapid) may alter the absorptive process of oral drugs (rate and extent) from the gut and, consequently, affects pharmacokinetics (PK) and pharmacodynamics (PD). Overall drug absorption is governed primarily by the slowest process, and, in such cases, gastric emptying is the rate-limiting step for absorption rate. Rapid and delayed gastric emptying may result in either predisposition to the development of adverse effects of drugs through enhanced peak exposures following rapid release from the stomach or decreased bioavailability and loss of effectiveness. The absorption of many drugs is therefore dependent on the rate of gastric emptying (2). Gastric emptying is the end-result of a complex sequence of

events, each of which depends on the other and controlled by neural and hormonal signals. Factors such as food, posture, pain and disease conditions, such as gastric ulcer, and metabolic conditions, such as diabetes, control gastric emptying (1,3,4). Most importantly, drugs such as alcohol, metoclopramide, erythromycin, domperidone, opiod analgesics and anticholinergics affect gastric emptying (5–9). These drugs act as agonists or antagonists of one or more of the endogenous hormones. Endogenous peptide hormones such as motilin and ghrelin stimulate gastric emptying, while cholecystokinin, peptide YY and glucagon-like peptide inhibit gastric emptying (10–12).

Enteral nutrition is very important for critically ill patients. Enteral nutrition compared to parenteral nutrition is cheaper and more effective and is associated with lower morbidity and mortality rates (13). Enteral feeding is often initiated within 24 h of admission of critically ill patients at intensive care units (14). Unfortunately, following initiation of EN, some patients become intolerant primarily due to gastrointestinal motility dysfunction associated with high gastric residual volume (GRV) and delayed gastric emptying (15,16). These patients often have increased risk of aspiration, lengthy intensive care unit (ICU) stay and higher mortality rates (14,17). It has been shown that patients that are intolerant to enteral nutrition do benefit from the administration of drugs that stimulate gastric emptying, often known as prokinetic agents such as erythromycin and metoclopramide (14–17). It has been recommended that the GRV is monitored in critically ill patients on enteral nutrition as a way of monitoring gastric emptying, and, whenever this is high, therapy with a prokinetic agent is recommended (14–17). Unfortunately, the most widely used prokinetic agents (erythromycin and metoclopramide) are still used as an "off-label" indication, and, therefore, there is an urgent need for a safe and efficacious gastric emptying prokinetic agent.

There are three main methods for studying gastric emptying: scintigraphy, ^{13}C-octanoic acid breath test and acetaminophen absorption test. Scintigraphy involves administration of a radiolabelled test meal, measurement of the radioactive substance around the stomach region and expression of the remaining activity in the stomach at each time point as a percentage of the initial activity which is then used as a measure of gastric emptying (18–22). Scintigraphy is the gold standard for measuring gastric emptying; however, because of the radiation exposure, it cannot be used in women and children; it is also very expensive and not universally available. The ^{13}C-octanoic acid breath test involves administration of a test meal containing a marker (^{13}C in octanoic acid) which is rapidly absorbed in the gut and metabolised in the liver to $^{13}CO_2$ and collection and analysis of breath samples at time intervals after ingestion for ^{13}C isotopic enrichment, and the final result is expressed as percentage of total activity recovered per unit time (23–27). This method is cheaper and safer compared to scintigraphy; however, it is not a direct measurement of gastric emptying, and the analysis can be difficult (28,29). The acetaminophen emptying test involves using acetaminophen absorption as an indirect measurement of gastric emptying after administration of a liquid meal. This is based on the principle that orally administered acetaminophen is poorly absorbed in the stomach and rapidly absorbed in the small intestine, and gastric emptying is therefore the rate-limiting step in the absorption of acetaminophen (2). Usually patients/volunteers receive doses of acetaminophen in a liquid meal and the concentration of acetaminophen in plasma samples taken at frequent intervals determined (2,13). Pharmacokinetic parameters such as the area under plasma concentration-time curve (AUC), the maximum plasma concentration (Cmax) and the time to maximum plasma concentration (Tmax) are derived (14,15,17). Simultaneous scintigraphy and acetaminophen emptying test have also been performed (19,20,30).

Data collected during pharmacokinetic and pharmacodynamic experiments are often described using nonlinear mathematical models. These models can be empirical or mechanistic (also known as physiologically based models) (31). The use of models during drug development has increased considerably in the last two decades, and the recent critical path document released by the US FDA emphasized the importance of model-based drug development (32). Adequate model development is central to making important decisions such as dose optimisation and also for designing future experiments (33). The mixed effects modelling approach, also known as the population approach, is now widely used in the analysis of pharmacokinetic and pharmacodynamic data. This approach has been described as the study of variability in plasma drug concentrations between individuals when standard dosage regimens are administered (34).

The aim of this paper was to comparatively evaluate gastric emptying function using the acetaminophen emptying test in patients with limited GRV and in those with increased GRV and to subsequently determine if prokinetic therapy improves gastric motility in patients with intolerance using a semi-mechanistic model based on a mixed effects modelling approach.

MATERIALS AND METHODS

Study Design

Acetaminophen plasma concentration data (Fig. 1) was obtained from a previous study designed to evaluate gastric

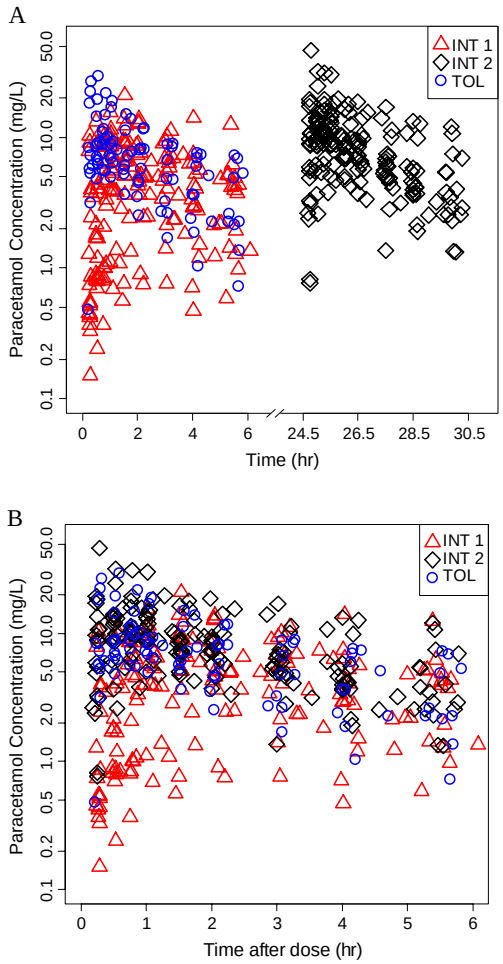

Fig. 1 Plots of acetaminophen plasma concentration *vs.* time (**A**) and acetaminophen plasma concentration *vs.* time after dose (**B**).

emptying in patients with limited GRV (tolerant) and GRV greater than or equal to 150 ml (intolerant) and whether prokinetic therapy (erythromycin and metoclopramide) improves gastric motility in intolerant patients. The data were analysed using a non-compartmental approach, and parameters such as peak plasma concentration (Cmax), concentration at 60 min (C60), time to Cmax (Tmax), area under the concentration time curve from 0 to 60 min (AUC0-60) and area under the concentration time curve from 0 to 360 min (AUC0-360) were derived. A detailed description of this study is presented in Landzinski *et al.* (14) and MacLaren *et al.* (16).

A schematic description of the study design is presented in Fig. 2. ICU patients on enteral nutrition were recruited into the study. Following recruitment, GRV was evaluated, and patients with GRV greater than or equal to 150 ml within the 24 h preceding enrollment were defined as intolerant, while patients with GRV less than 150 ml were defined as tolerant. Within 6 h of study enrollment, all patients received 975 mg of undiluted acetaminophen syrup. Enteral nutrition was then temporarily suspended for 6 h, during which plasma concentration was determined at 10, 30, 45, 60, 90, 120, 180, 240 and 360 min after acetaminophen administration. Patients in the intolerant arm of the study were randomized into two groups where they received treatment with a prokinetic agent (erythromycin or metoclopramide). Erythromycin 250 mg or metoclopramide 10 mg was administered intravenously every 6 h after the last acetaminophen plasma sample was collected. Thirty min after the fourth dose of the prokinetic agents, another dose of acetaminophen (975 mg) was administered, and plasma concentration was also determined at 10, 30, 45, 60, 90, 120, 180, 240 and 360 min after acetaminophen administration. In this work, intolerant groups before and after administration of prokinetic agents were coded INT 1 and INT 2, respectively, and the tolerant group was coded TOL. In the end, 10 and 20 patients were recruited into the tolerant and intolerant arms of the study, respectively. Equal numbers of patients in the intolerant group were randomized to the erythromycin or metoclopramide.

Data Analysis

Two types of model were investigated in this paper. The first class of model investigated was a three-compartment model (conventional two-compartment first-order absorption and elimination model) described in Fig. 3a. The three compartments represent the depot, central and peripheral compartments. This model is coded model 3 (for three compartments) in this paper. The structural model parameters in this model are ka (absorption rate constant), V1 (volume of central compartment), V2 (volume of peripheral compartment), CLD (intercompartmental clearance) and CL (clearance).

The second class of model is a semi-mechanistic four-compartment model which is similar to the three-compartment model with a separate compartment added for the stomach. Thus, the four compartments represent stomach, intestine, and central and peripheral compartments. This model is described in Fig. 3b and is coded model 4 (for four compartments) in this paper. The structural model parameters in this model are kg (gastric emptying rate constant), ka, V1, V2, CLD and CL. Parameter kg represents the rate of emptying of the contents of the stomach into the small intestine.

Model 3A is based on model 3 with a single ka estimated for all the groups i.e. INT 1, INT 2 and TOL. Model 3B has two ka: ka1 for INT 1 and ka2 for INT 2 and TOL. Model 3C has three ka: ka1 for INT 1, ka2 for INT 2 and ka3 for TOL. Model 3D has four ka: ka1 for INT 1, ka2 for INT2_ERY (intolerant group on erythromycin), ka3 for INT2_MET (intolerant group on metoclopramide) and ka4 for TOL.

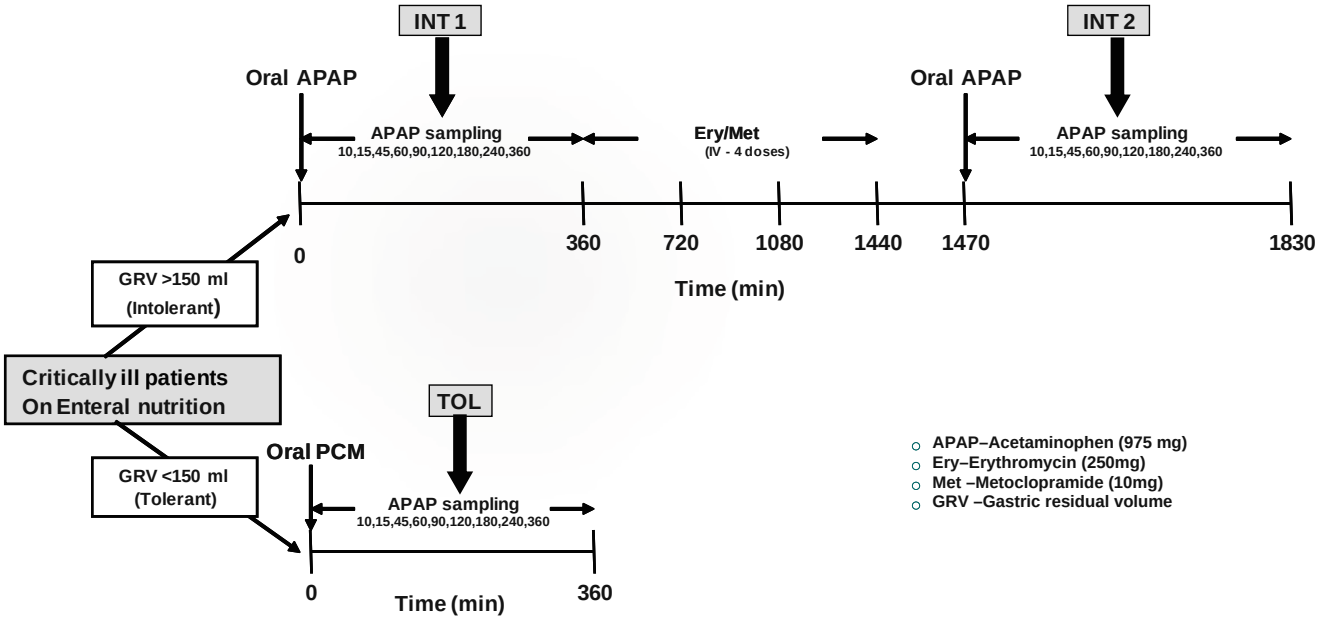

Fig. 2 Schematic description of the study design.

Model 4A is based on model 4 with a single kg estimated for all the groups, i.e. INT 1, INT 2 and TOL. Model 4B has two kg: kg1 for INT 1 and kg2 for INT 2 and TOL. Model 4C has three kg: kg1 for INT 1, kg2 for INT 2 and kg3 for TOL. Model 4D has four kg: kg1 for INT 1, kg2 for INT2_ERY (intolerant group on erythromycin), kg3 for INT2_MET (intolerant group on metoclopramide) and kg4 for TOL. These models are also described in Table I.

Population parameter values were estimated using a nonlinear mixed effect modelling approach in NONMEM version 7 using FOCE with INTERACTION option (35).

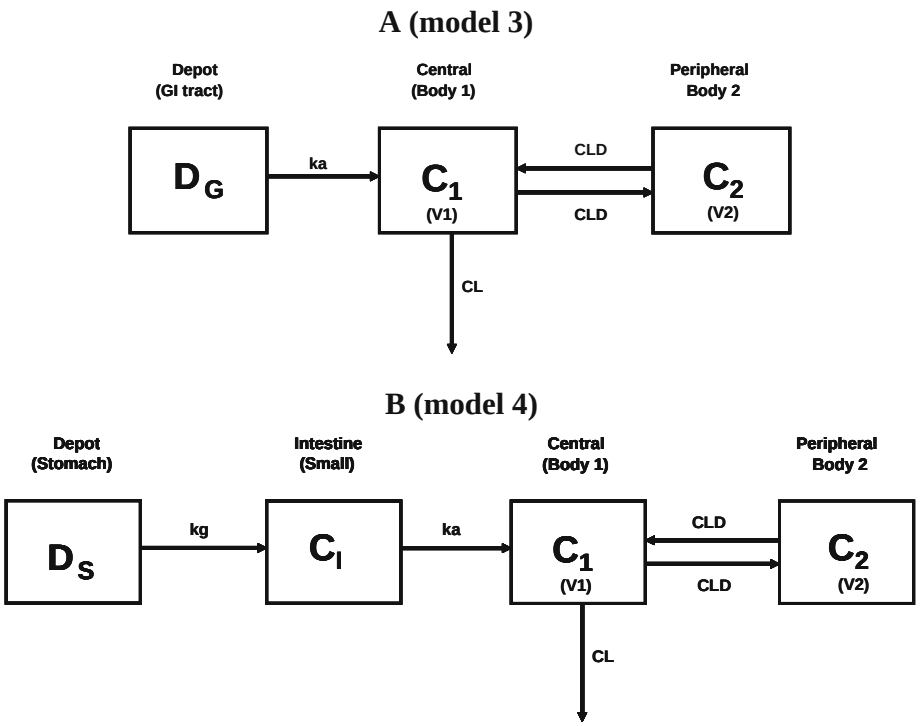

Fig. 3 Conventional two compartment first-order absorption model (**A**) and two-compartment first-order absorption model with an extra compartment for stomach (**B**).

Table I Table of Different Models Investigated During the Population PK Analysis

Model	Code	# of compartment	Description	# of parameters	Objective function	
					Value	Δ
three-compartment model	3A	3	ka = INT 1, INT 2, TOL	11	1387.120	–
	3B	3	ka1 = INT 1 ka2 = INT 2, TOL	12	1183.351	203.769
	3C	3	ka1 = INT 1 ka2 = INT 2 ka3 = TOL	13	1181.723	205.397
	3D	3	ka1 = INT 1 ka2 = INT2_ERY, ka3 = INT2_MET, ka4 = TOL	14	1175.255	211.865
four-compartment model	4A	4	kg = INT 1, INT 2, TOL	13	1343.698	43.422
	4B	4	kg1 = INT 1 kg2 = INT 2, TOL	14	1133.015	254.105
	4C	4	kg1 = INT 1 kg2 = INT 2, kg3 = TOL	15	1132.328	254.792
	4D	4	kg1 = INT 1 kg2 = INT2_ERY, kg3 = INT2_MET, kg4 = TOL	16	1130.719	256.401

Both between-subject and residual variability (random effects) and typical parameter values (fixed effects) were estimated. Only models that successfully minimized were considered, and the covariance step was not required *a priori*. A drop in objective function value of 3.84, equivalent to a significance level of 0.05 for each additional parameter, was required before the more complex model was considered. Visual inspection of diagnostic plots and individual concentration plots was also used to support model selection.

A nonparametric bootstrap analysis of the final model was undertaken using Peal-speaks-NONMEM (PsN) (36,37). One-thousand bootstrap replicates were sampled from the original data using each individual's datasets as the sampling unit, and the mean and standard deviation of the resulting parameter estimates were calculated.

The equations for the final model are

$$y_{ij} = f\left(\theta_i, t_{ij}\right) \cdot e^{\varepsilon_{ij}} \tag{1}$$

where y_{ij} is the observed acetaminophen plasma concentration for the i^{th} individual at the j^{th} time, t_{ij}. ε_{ij} is the residual error at the time t_{ij} and $\varepsilon_{ij} \sim N(0,\sigma^2)$. The differential equations are given by

$$\begin{aligned}
\frac{dA_1}{dt} &= -kg \cdot A(1) \\
\frac{dA_2}{dt} &= kg \cdot A(1) - ka \cdot A(2) \\
\frac{dA_3}{dt} &= ka \cdot A(2) + k21 \cdot A(4) - ((k12 + kel) \cdot A(3)) \\
\frac{dA_4}{dt} &= k12 \cdot A(3) - k21 \cdot A(4)
\end{aligned} \tag{2}$$

where $f(\theta_i,t_{ij}) = A(3)/V1$, $kel = CL/V1$, $k12 = CLD/V1$ and $k21 = CLD/V2$.

$$\theta_i = \theta \cdot e^{b_i} \tag{3}$$

where θ_i is vector of individual parameter estimates, θ is the vector of population parameter estimates (typical individual and fixed effect parameter estimates), and b_i is the vector of individual deviations from the population parameter estimates (random effect parameter estimates).

$$\theta = [kg, ka, CL, V1, V2, CLD] \tag{4}$$

and $b_i \sim N(0, \Omega)$, where Ω is a diagonal element matrix with the elements as the variances of the interindividual variabilities (IIV) of the individual parameters. The model that was fitted during the analysis is the analytical solution to the differential equations described above (Eq. 2).

RESULTS

The different models investigated are presented in Table I. The best model was model 4B, a four-compartment model with two gastric emptying rate constants: kg1 for INT 1 and kg2 for INT 2 and TOL. The between-subject variabilities and residual error variability were estimated using an exponential variance model. Attempts to include a full variance–covariance matrix in the model resulted in stability issues, and the final model only has diagonal elements.

The final parameter estimates obtained from the analysis together with the standard errors expressed as percentage

relative standard errors (%RSE) are presented in Table II. This table also includes the estimates and the %RSE obtained from the bootstrap analysis. Of the 1000 bootstrap replicates, 816 resulted in successful minimization, and 374 resulted in successful minimization with a successful covariance step implemented. The replicates with successful minimization were used for the analysis with the %RSE obtained from the standard deviation of the individual estimates. Plots of the observed *versus* population-predicted and observed *versus* individual-predicted for the final model (model 4B) are shown in Fig. 4. Figure 5 shows the plots of the conditional weighted residuals *versus* time and the conditional weighted residuals *versus* population-predicted acetaminophen plasma concentrations. Figure 6 shows acetaminophen plasma concentration *versus* time data points overlaid with the plots of the population prediction *versus* time for the different groups (INT 1 and 2 and TOL). The predictive performance of the final model (model 4B) was assessed using the visual predictive check (VPC), and the results are presented in Fig. 7. The VPCs were obtained by simulating plasma concentration using the final model (model 4B) and the parameter estimates in Table II at time points selected between the sampling region (0–6.5 h and 24.5–31 h with a step size of 0.1). Ten-thousand plasma concentrations were simulated for each time points and for each time points the fifth, fiftieth (median) and the ninety-fifth percentiles were generated. Plots of the fifth, fiftieth and the ninety-fifth percentiles (90% prediction interval) *versus* time are overlaid with the acetaminophen plasma concentration *versus* time data points. Figure 8 shows plots of absorption rate constant for model 3B *versus* gastric emptying rate constant for model 4B and absorption rate constant for model 3B *versus* absorption rate constant for model 4B.

Plots in Fig. 5 (weighted residual *versus* time and weighted residual *versus* predicted concentration) did not reveal any systematic bias in the model prediction. Figure 6 also shows that the population-predicted line is through the data. Plots of the visual predictive check based on the 90% prediction interval using the final model (model 4B) in Fig. 7 show adequate coverage, confirming the ability of the model to predict acetaminophen plasma concentrations similar to the original data for the different groups, i.e. INT 1 and 2 and TOL with approximately 5% of points outside the interval. The results of the bootstrap analysis also confirmed the robustness of the final parameter estimates.

DISCUSSION

This analysis has described a semi-mechanistic model for the population PK analysis of acetaminophen data obtained from critically ill patients tolerant and intolerant to EN. This represents the first attempt to develop a population PK model for such group of patients. Delayed gastric emptying which occurs as a result of reduced gastric motility and increased residual volume is a serious problem in this group of patients, especially for patients that become intolerant following initiation of EN. Prokinetic drugs that increase gastric motility, such as erythromycin and metoclopramide, have been shown to be beneficial in these patients; however, there is a concern about the "off-label" use of these drugs. Erythromycin is primarily used as an antibiotic and has side effects due to gastrointestinal disturbances, such as diarrhoea, abdominal pain, nausea and vomiting, and metoclopramide is primarily used as an antiemetic and for treatment of migraine headaches with side effects mostly associated with its exrapyramidal effects. There is, therefore, an urgent need for development of drugs that are safe and effective for the treatment of delayed gastric emptying.

The data used for this analysis were obtained from a previous study that was used to evaluate gastric emptying in tolerant and intolerant patients on enteral nutrition and

Table II Parameter Estimates for the Final Model; Model 4B (Four-Compartment Semi-mechanistic Model)

Parameter	Final model		Bootstrap	
	Estimate (%RSE[a])	IIV[b] (%RSE)	Estimate (%RSE) [90% CI[c]]	IIV (%RSE) [90% CI]
kg1 (hr^{-1})	1.30 (53.84)	3.32 (40.96)	1.25 (51.75) [0.60–2.79]	3.02 (45.21) [1.37–5.70]
kg2 (hr^{-1})	27.8 (59.35)		25.75 (58.20) [10.11–60.06]	
ka (hr^{-1})	5.12 (28.13)	1.18 (41.19)	5.21 (39.02) [3.17–9.72]	1.15 (42.92) [0.54–2.16]
CL (L/h)	13.0 (19.62)	0.598 (45.82)	12.36 (21.95) [7.89–16.42]	0.55 (55.01) [0.21–1.26]
V1 (L)	63.8 (12.79)	0.365 (39.18)	63.72 (12.68) [50.50–77.41]	0.32 (44.38) [0.14–0.61]
CLD (L/h)	22.6 (19.78)	0.0152 (327.6)	24.1 (23.76) [15.65–33.22]	0.00027 (194) [0.00015–0.16]
V2 (L)	69.0 (38.70)	1.39 (36.76)	78.92 (45.21) [39.57–155.13]	1.19 (55.50) [0.39–2.71]
σ (CV)	0.30 (7.43)	–	0.3 (7.17) [0.26–0.33]	–

[a] percentage relative standard error, [b] variance, [c] 90% non-parametric confidence interval

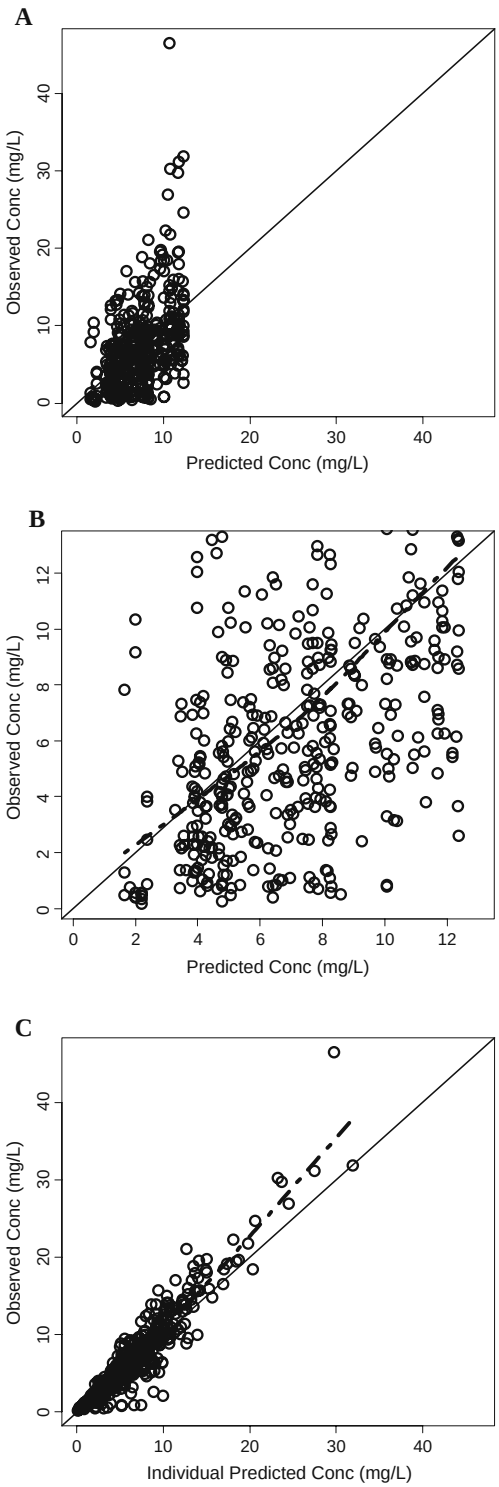

Fig. 4 Plots of observed *vs.* population-predicted (**A**, **B**) and observed *vs.* individual-predicted (**C**) acetaminophen concentrations for model 4B (four-compartment semi-mechanistic model with two gastric emptying rate constants). *A* = All data, *B* = Reduced limits.

whether prokinetic therapy improves gastric motility in intolerant patients. Figure 1 shows that there is a considerable amount of variability in the data, especially during the absorption phase, and that the plasma concen-

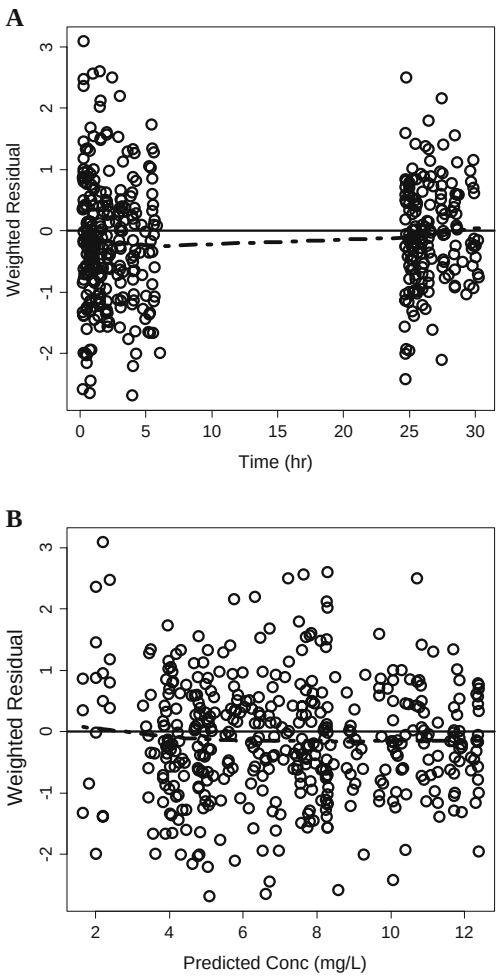

Fig. 5 Plot of the weighted residuals *vs.* time (**A**) and plot of weighted residuals *vs.* population-predicted acetaminophen concentrations (**B**) for the final model (model 4B). The dashed line is a smooth line through the data.

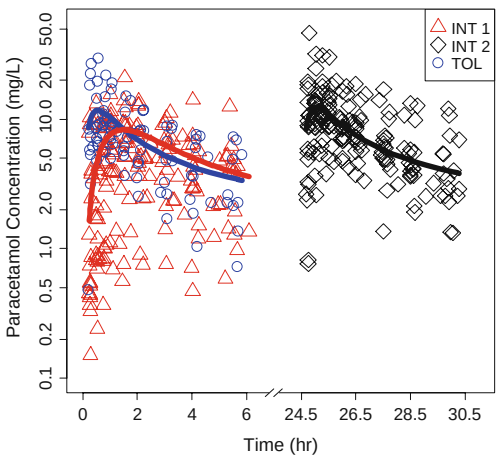

Fig. 6 Plot of data and population predictions for INT 1, INT 2 and TOL data.

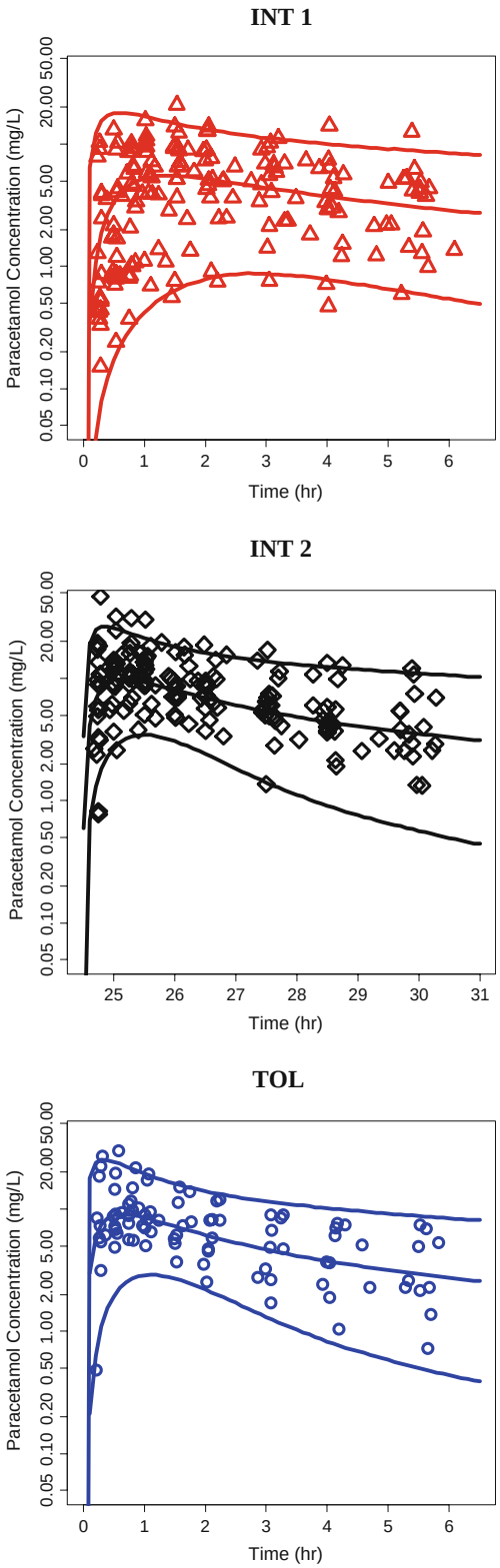

Fig. 7 Plots of visual predictive check for the different groups (INT 1, INT 2 and TOL). The lines represent 5th, 50th and 95th percentiles, and symbols are the observed acetaminophen concentrations.

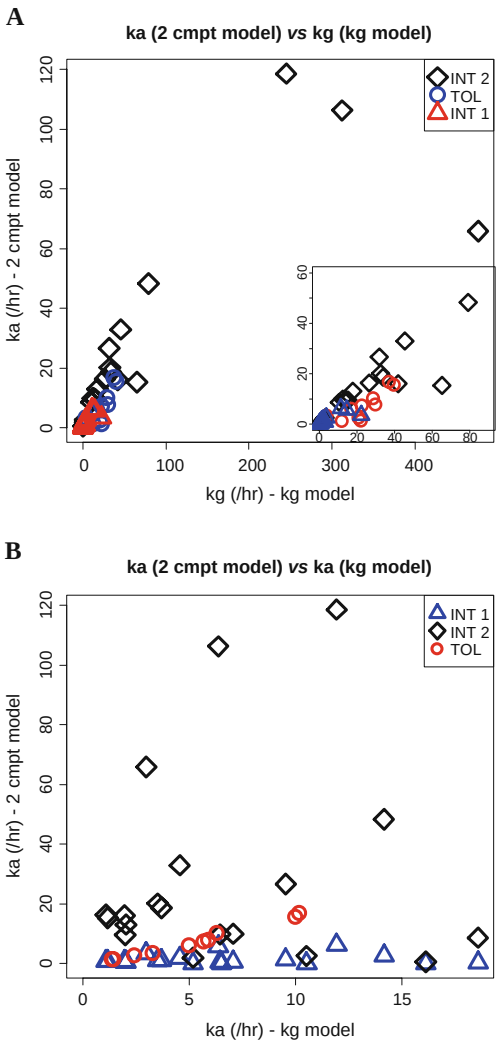

Fig. 8 Plots of absorption rate constant for model 3B *versus* gastric emptying rate constant for model 4B (**A**) and absorption rate constant for model 3B *versus* absorption rate constant for model 4B (**B**).

tration data obtained for INT 1 (intolerant patients before treatment) are generally lower than those obtained for INT 2 (intolerant patients after treatment) and TOL (tolerant patients), again especially during the absorption phase. Therefore, efforts to improve the fitting were mostly focused on the absorption phase.

Table I shows the objective function obtained for the different models investigated. A three-compartment model based on the conventional two-compartment first-order absorption and elimination model (model 3) and a four-compartment semi-mechanistic model similar to the conventional three-compartment first-order absorption and elimination model but with an extra compartment introduced for the stomach (model 4) were investigated. Model 3A, which is based on model 3 with a single absorption rate constant estimated for the groups (INT 1 and 2 and TOL), was used as the reference model. Model 3B, which is also

based on model 3 but with two absorption rate constants: ka1 for INT 1 and ka2 for INT 2 and TOL, showed a significant improvement on model 3A with a change in objective function of 203.769 with an additional parameter. Estimating different absorption rate constants for the groups, i.e. INT 1, INT 2 and TOL as in model 3C, also showed a significant improvement on model 3A (objective function change = 205.397 with two additional parameters) but not on model 3B (objective function change = 1.63 with an additional parameters). Introducing treatment effect to the group that was treated with prokinetic agents, i.e. INT, 2 by estimating different absorption rate constants for patients on erythromycin and those on metoclopramide as in model 3D showed a significant improvement on model 3A (objective function change = 211.865 with three additional parameters) and on models 3B and 3C (objective function change = 8.096 with two additional parameters and objective function change = 6.468 with an additional parameter, respectively). Model 4A, which is based on model 4 with a single gastric emptying parameter for the groups (INT 1 and 2 and TOL), showed an improvement on model 3A (objective function change = 43.422 with two additional parameters) and worse than model 3B (objective function change = −160.34 with an additional parameter). Model 4B, which estimates two different gastric emptying parameters: kg1 for INT 1 and kg2 for INT 2 and TOL, showed significant improvement on model 3A (objective function change = 254.105 with three additional parameters) and 4A (objective function change = 210.683 with an additional parameter). Estimating different gastric emptying rate constants for the groups, i.e. INT 1, INT 2 and TOL, as in model 4C, also showed a significant improvement on model 3A (objective function change = 254.792 with four additional parameters) but not on model 4B (objective function change = 0.687 with an additional parameter). Also introducing treatment effect to the group that was treated with prokinetic agent, i.e. INT 2, by estimating different gastric emptying rate constants for patients on erythromycin and those on metoclopramide, as in model 4D, only showed a significant improvement on model 3A (objective function change = 256.401 with four additional parameters) and not on model 4B (objective function change = 2.296 with two additional parameters). The best model is, therefore, model 4B. This shows that adding an additional compartment for the stomach to the conventional two-compartment first-order absorption model and estimating two rate constants (one for INT 1 and the other one for INT 2 and TOL) is important for the fitting. It also shows that there is no difference between the intolerant patients after therapy with prokinetic agents and tolerant patients, which means prokinetic agents help the intolerant patients to become tolerant. The parameter estimates obtained from the final model correspond to mean gastric emptying half times of about 0.53 h for INT 1 and 0.025 h for INT 2 and TOL groups. The gastric emptying half-time was improved by a factor of about 20 in the intolerant patients after therapy with prokinetic agents. The results confirmed that intolerant patients on enteral nutrition benefit from off "label-label" use of prokinetic agents erythromycin and metoclopramide. The results also showed that the doses of erythromycin and metoclopramide used in this study were able to improve the gastric emptying half-life to the same levels as tolerant patients, which are the control group in the study. The results also showed that there is no difference between the two prokinetic agents (erythromycin and metoclopramide) in terms of facilitating gastric emptying and tolerance to enteral nutrition. These conclusions are consistent with the results of Landzinski *et al.* (14,17) based on analysis of this data using a non-compartmental approach based on parameters such as Cmax, C60, Tmax, AUC0-360 and AUC0-60. It was concluded that the two prokinetic agents significantly increase Cmax, C60, AUC and shortened Tmax. However, unlike MacLaren *et al.* (15,16), who suggested that erythromycin may be more effective than metoclopramide, this analysis showed that there is no difference between the two prokinetic agents in terms of effectiveness on the rate of gastric emptying. Figure 8 shows plots of absorption rate constant for model 3B *versus* gastric emptying rate constant for model 4B and absorption rate constant for model 3B *versus* absorption rate constant for model 4B. These plots show the relationship between the absorption parameters (gastric emptying rate constant and absorption rate constant) between the best model based on the conventional two-compartment first-order absorption and elimination model (model 3B) and the best model based on the new semi-mechanistic four-compartment first-order absorption model. These plots show that the estimates for the absorption rate constant in a conventional two-compartment first-order absorption and elimination model correlate more with the estimates for the rate of gastric emptying in the semi-mechanistic four-compartment model compared with estimates for the absorption rate constant in the semi-mechanistic four-compartment model.

Figures 4a and b show the plot of observed concentration *versus* population prediction for the final model (model 4B), showing that there is a considerable variability in the data with almost equal number of points on either side of the line of unity, and a smooth line through the data is very close to the line of unity. A plot of observed concentration *versus* individual prediction (Fig. 4c) shows good agreement between the two with the points close to the line of unity especially at low concentrations.

Consequently, the final model is a four-compartment semi-mechanistic model for stomach, intestine, central and peripheral compartments. This model is similar to the

model described by Clements *et al.* (19,20) for the PK of acetaminophen absorption and gastric emptying in human. Clements *et al.* (19,20) fitted the same type of model to measurements obtained simultaneously from scintigraphy (to measure gastric emptying) and plasma concentration of acetaminophen. Clements *et al.* (19,20) proposed a four-compartment model because gastric emptying is the rate-limiting step in the absorption of acetaminophen, and, therefore, gastric emptying governs the absorption of acetaminophen. They also observed the same relationship that has been observed in this work between estimates for the absorption rate constant from conventional two-compartment first-order absorption and elimination model and the four-compartment model.

CONCLUSION

A semi-mechanistic model has been described for the population PK of acetaminophen in critically ill patients tolerant and intolerant to EN. This model separates stomach from intestine, and the resulting four-compartment model provides a better fit to the data compared with the equivalent conventional model. This model adequately described the data in these groups of patients and will help in the development of future prokinetic drugs in terms of study design and simulation. The results obtained showed that gastric emptying half-time is improved by a factor of about 20 in the patients that are intolerant to enteral nutrition after treatment with prokinetic agents, erythromycin or metoclopramide.

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