

# Quantifying Pain Relief Following Administration of a Novel Formulation of Paracetamol (Acetaminophen)

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*This article describes how a model-based analysis was used to aid development of a novel formulation technology. Paracetamol (acetaminophen) was used as the motivating example with 4 different formulations (2 developmental and 2 commercial) compared using stochastic (Monte Carlo) pharmacokinetic (PK)–pharmacodynamic (PD) simulations to explore potential differences in pharmacodynamic outcomes. PK models were developed from data collected during an intensively sampled, 4-arm crossover trial in 25 fasted healthy subjects, administered 1 g of paracetamol in 4 different formulations. The PK models were linked to a previously published PD model that quantified pain relief over time following tonsillectomy. The number needed to treat (NNT) was the primary numeric used to compare effectiveness.*

*The developmental formulations were likely to produce faster and greater analgesia with an NNT (compared with placebo) to reduce pain by 50% over a 45-minute interval post dose of 2.75 and 2.88 compared with 4.31 and 3.2 for the commercial products. Over the course of 1 hour, all formulations were comparable. The stochastic simulations provided support that the novel formulation technology was likely to provide a clinically meaningful advantage and should be developed further.*

**Keywords:** Paracetamol; pharmacokinetics; pharmacodynamics; pharmacometrics

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Researching new molecules and formulations that deliver optimal, efficacious clinical outcomes with minimal toxicity is a constant test for the drug development industry. Such challenges have resulted in fewer drugs being approved by regulatory authorities, rising development costs, and pipelines that are commonly reported as “dry.”<sup>1,2</sup> These trends were recognized by the US Food and Drug Administration (FDA) with the launch in March 2004 of its Critical Path Initiative following publication of a white paper titled “Innovation or Stagnation: Challenge and Opportunity on the Critical Path of New Medical Product Development.”<sup>3</sup> The purpose of this report was to “create an urgency with the

drug development enterprise to address the so-called productivity problem in modern drug development.”<sup>4</sup> In this document, a model-based drug development process was proposed to facilitate go-no-go decision making during drug development, in the anticipation that the development and application of pharmacokinetic (PK)–pharmacodynamic (PD) models would significantly improve cost effectiveness of drug development.

A more recent review by the director of the FDA Office of Clinical Pharmacology reinforced the advantages of model-based drug development<sup>4</sup> with several practical examples now presented in the scientific literature.<sup>5,6</sup> These case studies demonstrate how modeling has improved decision making in key areas such as clinical trial design, dosage selection, formulation optimization, and program termination. To date these examples have primarily been presented by large pharmaceutical companies; presumably because they have firsthand experience of the benefits that modeling can bring to the development process.<sup>7</sup> However, pharmaceutical scientists in other areas can also use these tools to inform decision making. This article describes how early PK data collected for various formulations of paracetamol were

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used with preexisting published PD literature to predict and compare pain relief scores following administration of various paracetamol (acetaminophen) formulations. The example is a practical application of how a model-based approach was used to help identify whether a novel oral drug delivery technology would translate into a clinically relevant benefit compared with existing commercial products, using paracetamol as an example.

## METHODS

To determine whether the novel formulation technology should be further developed, stochastic (Monte Carlo) techniques that included random effects on both PK and PD models were used to simulate 4 clinical trials, each of which consisted of 2500 subjects. For each trial, half the subjects were assigned placebo dosing with the other half assigned to receive 1 of 4 paracetamol formulations. The same seed number was used for all simulations, thereby replicating placebo subjects across the trials. The 4 paracetamol tablets evaluated were 2 products using an experimental formulation technology and 2 commercial products. Individual paracetamol concentration-time profiles were simulated for those who received paracetamol, together with individual pain relief status as a composite function of placebo and paracetamol effects. For subjects who were assigned placebo, pain relief was simulated as a function of placebo alone.

To conduct the simulations, PK models for each paracetamol formulation were needed together with a PD model for both drug and placebo effects. Statistical models describing the distribution of the between-subject variability and residual unexplained variability were also needed.

### Pharmacokinetic Models

The PK parameters used to simulate paracetamol concentrations were determined from a phase I clinical trial conducted in 25 fasted healthy subjects, designed to conform with the FDA "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products."<sup>8</sup> The trial was a randomized, single oral dose, 4-treatment, 4-period crossover design with a 1-week washout between doses. The 4 paracetamol tablet products studied were Tylenol Extra Strength Rapid Release Gels (Johnson & Johnson, Brunswick, NJ), Panadol Rapid caplets (GlaxoSmithKline, Boronia, Victoria, Australia), and 2 Imaginot (Brisbane, Queensland, Australia) formulations referred to as A and B. The

Imaginot formulations incorporated pH modulating and water uptake agents to produce ultrafast in vitro dissolution under a range of test methods representative of gut stasis, neutral pH, and a fed state (US patent application no 11/604,972). Both contained 200 mg of sodium bicarbonate per 500 mg of paracetamol compared with 630 mg for Panadol Rapid, whereas Tylenol contained no alkaline agent. Two tablets, each containing 500 mg of paracetamol, were swallowed with 170 mL of water.

Venous blood samples were collected from an indwelling catheter at 2, 5, 7, 8.5, 10, 12, 14, 17, 20, 25, 30, 45, and 60 minutes post dose. Additional samples were taken 2, 4, 6, and 8 hours post dose. Plasma was separated and held in frozen storage prior to assay. Drug concentrations were measured using high-performance liquid chromatography (Waters Millennium, Milford, Mass) with UV detection at 245 nm. A Waters C<sub>18</sub> 4 $\mu$  Radial Pak cartridge in an RCM 8  $\times$  10 Radial Compression Module with a Guard-Pak Nova-Pak C<sub>18</sub> precolumn module was used. Plasma samples were equilibrated at room temperature and vortexed for 10 seconds for sample preparation. Plasma (250  $\mu$ L), internal standard solution (50  $\mu$ L; 50  $\mu$ g/mL N-acetyl-m-aminophenol), distilled water (50  $\mu$ L), phosphate buffer pH 7.4 (100  $\mu$ L), and ethyl acetate (2.0 mL) were mixed for 5 minutes and then centrifuged at 3000 rpm for 5 minutes.

The organic layer was removed and the solvent evaporated at 37°C under a gentle air stream. The residue was reconstituted in 100  $\mu$ L of acetonitrile (0.08% in deionized water) used as the mobile phase and 10  $\mu$ L was injected onto the column held at 22°C with a flow rate of 2 mL/min. Retention times for paracetamol were in the range of 3.8 to 4.3 minutes and for the internal standard 6.4 to 7.3 minutes. The intraday coefficient of variation was 2.3%, 1.9%, and 5.3% at concentrations of 1.0, 5.0, and 20.0  $\mu$ g/mL, respectively. The interday coefficient of variation over 6 occasions was 6.1%, 2.9%, and 1.7% at the same 3 concentrations. The lower limit of quantification (LLQ) was 0.5  $\mu$ g/mL. Values below this were reported as 0 and removed from the analysis because only 0.177% of observations in the elimination phase were below the LLQ.

Paracetamol concentrations for each of the 25 subjects were modeled with the computer software Scientist.<sup>9</sup> The Akaike information criterion (AIC) was used to discriminate between models together with standard goodness-of-fit plots. No weighting of the residuals was used.<sup>10</sup> Individual estimates of the elimination and distribution parameters were determined for each subject using data from all formulations,

**Table I** Pharmacodynamic Model Parameters for Placebo Effect

	Parameter Value	Correlation		
		$\beta$	$T_{eqp}$ , h	$T_{elp}$ , h
$\beta$	1.54 (24)	1		
$T_{eqp}$ , h	1.96 (40)	0.304	1	
$T_{elp}$ , h	2.06 (50)	0.429	0.294	1

$\beta$ , magnitude of the placebo effect;  $T_{eqp}$ , half-life of equilibration;  $T_{elp}$ , half-life of elimination.

Parameter values obtained from Anderson et al<sup>11</sup> are represented as mean, with between-subject variability (as percentage coefficient of variation) shown in parentheses.

whereas absorption parameters and lag time were estimated individually for each formulation. The geometric means and variances were calculated from the results using a 2-stage approach. Visual predictive checks (VPCs) were conducted to determine whether the PK models could adequately capture the observed data. The VPCs were performed by simulating 2500 individuals from the parameter estimates and their variances, which were joined with a previously reported residual error model discussed further below. The median, 10th, and 90th prediction intervals were computed for each formulation, and the observed median, 10th, and 90th percentiles were overlaid onto the prediction intervals.

### Pharmacodynamic Models

A pain relief model and associated parameter estimates for both placebo and paracetamol effects were obtained directly from published literature.<sup>11</sup>

#### Placebo Effect

The placebo effect was characterized by a Bateman function and modeled as a fraction from 0 to 1, with 0 representing total pain relief and 1 representing no pain relief. Placebo effect was quantified by 2 rate constants describing the onset ( $K_{eqp}$ ) and elimination of effect ( $K_{elp}$ ).<sup>11</sup> The magnitude of effect ( $\beta$ ) was also incorporated such that placebo was represented by the following:

$$\text{Placebo Effect} = 1 - \beta \times \left( \frac{K_{eqp}}{(K_{eqp} - K_{elp})} \times (e^{-K_{elp}t} - e^{-K_{eqp}t}) \right)$$

The placebo effect model parameters are shown in Table I, where  $K_{eqp}$  and  $K_{elp}$  are represented as their corresponding half-lives  $T_{eqp}$  and  $T_{elp}$ , respectively. During the simulation experiments it was

**Table II** Pharmacodynamic Model Parameters for Paracetamol Effect

	Parameter Value	Correlation		
		$E_{max}$ , U	$EC_{50}$ , mg/L	TEQ, min
$E_{max}$ , U	0.517 (64)	1		
$EC_{50}$ , mg/L	9.98 (107)	0.075	1	
TEQ, min	53 (217)	0.206	0.690	1
Residual error, U	SD = 1.2	—	—	—

$E_{max}$ , maximum effect (from 0 to 1);  $EC_{50}$ , concentration at which 50% of the maximum effect is seen; TEQ, equilibration half-life into the effect compartment. Parameter values obtained from Anderson et al<sup>11</sup> are represented as mean, with between-subject variability (as percentage coefficient of variation) shown in parentheses.

possible for the placebo effect to not be constrained between 0 and 1 because of the inclusion of random effects. When this occurred, a new set of parameters were resampled from their distributions.

#### Paracetamol Effect

The paracetamol effect on pain was similarly modeled as a fraction from 0 to 1, with 0 representing total pain relief and 1 representing no pain relief. Pain scores were quantified by an  $E_{max}$  model with the change in pain score from baseline delayed by use of an effect compartment.<sup>12</sup> Pain relief for paracetamol was quantified by the following expression:

$$\text{Paracetamol Effect} = 1 - \left( \frac{E_{max} \times Ce}{EC_{50} + Ce} \right)$$

where  $Ce$  is the effect compartment concentration dependent on the equilibration half-life (TEQ),  $E_{max}$  is the maximum drug effect, and  $EC_{50}$  is the concentration that results in 50% of the maximum drug effect. The paracetamol effect model parameters are shown in Table II. As with the placebo model, individual parameters were resampled from their distributions if the paracetamol effect was not constrained between 0 and 1.

Pain was quantified as a score from 10 to 0 with initial pain fixed to 10 for all subjects. The change in pain was computed by joining the models for placebo and paracetamol effects,<sup>11</sup> such that

$$\text{Pain} = 10 \times \text{Paracetamol Effect} \times \text{Placebo Effect}$$

Random effects describing between-subject variability were included in the model under the assumption that the parameter of interest was log normally distributed,

$$P = POPP \times e^{(PPVP)}$$

where  $P$  is the individual parameter of interest,  $POPP$  is the population estimate of the parameter of interest, and  $PPVP$  is a random effect with a mean of 0 and variance of  $\Omega$ .

The PK model was linked to a previously reported Random Unexplained Variability (RUV) model and consisted of additive and proportional terms estimated to be standard deviation (SD) = 1.05 mg/L and constant coefficient of variation (CCV) = 6.4%, respectively.<sup>11</sup> The RUV for the PD model was again directly obtained from the previously reported PD model<sup>11</sup> and described by an additive term estimated to be SD = 1.2 units (Table II).

## Clinical Significance

To determine whether the formulation technology should be further developed, the number needed to treat to benefit 1 subject (NNTB) for each paracetamol formulation versus placebo was computed as the inverse of the absolute risk reduction (ARR), where

$$ARR = \text{Absolute Risk}_{\text{Placebo}} - \text{Absolute Risk}_{\text{Treatment Group}}$$

The 95% confidence interval (CI) for NNTB was also computed, and where this value indicated that placebo was superior to the test formulation (ie, the CI included a negative number), the CI was represented as a range from the number needed to treat to harm 1 patient (NNTH) as described by Altman.<sup>13</sup>

The NNTB was computed for the following 3 clinical end points:

1. A change in pain relief of 50% or more over a 10-, 15-, 30-, and 45-minute interval post dose as well as a 1-, 2-, and 4-hour interval post dose (ie, a pain score of  $\leq 5$  at any point over this duration). This method was chosen in part so that pain relief would be conditional upon a prior score, which might be applicable to headache relief, for example.
2. A change in pain relief of 95% over an 8-hour interval post dose.
3. The proportion of subjects with 40%, 50%, 60%, 70%, and 80% pain relief over a 15-minute, 30-minute, 45-minute, and 60-minute interval post dose.

Plasma concentrations, placebo, and drug effect scores were simulated every 3 minutes over a 12-hour interval post dose. Because of numerical instability linking prior PD model parameters from Anderson et al<sup>11</sup> with alternative PK parameters, TEQ was fixed to the population estimate of 53 minutes with no

between-subject variability. All simulation details and end point evaluations were prespecified in a statistical analysis plan.

NONMEM version V release 1.1<sup>14-16</sup> was used to simulate the data with the Compaq Visual Fortran compiler (version 6.1 update C). The computation platform used Pentium IV 3.2 GHz processors running under Windows XP. Wings for NONMEM (version 407)<sup>17</sup> was used to control the process. Parameters were resampled if they were outside 99.95% of the specified distribution, which corresponds to a  $z$  statistic of 3.27 from the normal distribution. The purpose of this approach was to prevent sampling from the extremes of the distributions.

## RESULTS

### Pharmacokinetics

The best PK model to fit the data was a 2-compartment linear elimination model with absorption described by a first-order input following a lag time. Differing structural models including 3-compartment models with variable inputs could not be supported by the data. The AIC for the final model was much lower than the best competing 1-compartment model (AIC = 2144 vs 4588, respectively). The final PK model parameters for the 4 paracetamol products are shown in Table III. The models described the data with reasonable precision and minimal bias based upon the individual plots (an example for 1 subject is shown in Figure 1) and VPCs (shown in Figure 2). The VPCs suggest that the observed and model simulated median values were closely aligned over the duration of the dosing interval for Imaginot A, Tylenol, and Panadol. The model-predicted median value for Imaginot B appeared to peak later than the observed data. There appeared to be a double peak for the 90th percentile for Tylenol. Generally, the 90th model prediction was slightly delayed compared with the observed data for all compounds, apart from Panadol Rapid. The VPCs also suggested that  $C_{\max}$  appeared to be slightly underpredicted for Imaginot A and B. The discrepancies between observed percentiles and prediction intervals were considered to be acceptable, with differences within each formulation considered negligible compared with differences between formulations.

### Pharmacodynamics

The simulated median pain relief scores over time for each paracetamol formulation are shown in Figure 3A. The plots indicate that the placebo effect is substantial with the only potential difference in



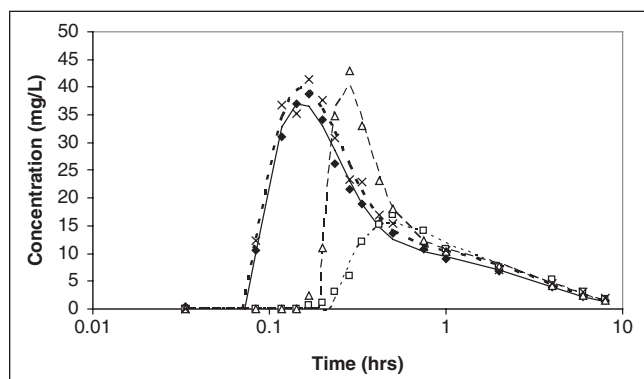


Figure 1. Measured and predicted paracetamol plasma concentrations. Symbols represent the measured concentration with lines representing the model predicted concentration, where  $\diamond$  and — represent Imaginot A,  $\times$  and .... represent Imaginot B,  $\square$  and --- represent Tylenol, and  $\Delta$  and — — represent Panadol Rapid.

pain relief scores between paracetamol formulations evident at 0 to 30 minutes post dose. A plot showing the difference between Imaginot A and Panadol is shown in Figure 3B.

### Clinical Significance

Estimated NNT values to reduce pain by 50% over different time points are presented in Table IV. Imaginot A and B had lower NNT values compared with Tylenol and Panadol Rapid over the first 10 minutes post dose, although the values were large and not convincing from a clinical perspective. Over the first 15 minutes, however, the NNT dropped significantly, with Imaginot A and B appearing to be preferred over the 2 commercial products. This trend continued over the course of 30 minutes post dose, after which little difference between the formulations was evident.

The NNT for 95% pain relief over an 8-hour post dose interval is also shown in Table IV, with no apparent differences between the formulations.

The proportion of subjects who had 40% to 80% pain relief over a 15-, 30-, 45-, and 60-minute post dose interval for the 4 paracetamol formulations are shown in Figure 4. For each plot, the percentage of subjects who achieved the specified pain reduction (y axis) is plotted against various pain reductions (x axis). At 15 minutes, it can be seen that Imaginot A and B had more subjects with 40% pain relief compared with Tylenol and Panadol Rapid. However, only about 14% of subjects actually achieved 40% pain relief at this time, which declined as the requirement for percentage pain relief increased. Little difference was visually identifiable when 70%

pain relief was evaluated. At 30 minutes, all paracetamol formulations had improved effectiveness at reaching the defined end points. There was also a greater difference between the Imaginot formulations and Tylenol, with Panadol Rapid sitting between the Imaginot and Tylenol formulations. The differences at 45 minutes were less pronounced than 30 minutes and further declined by 60 minutes post dose.

### DISCUSSION

This article demonstrates how a model-based approach was used to help determine whether a novel formulation technology should be further developed by a small pharmaceutical company. The work was undertaken using paracetamol as a motivating example and has sought to demonstrate the utility of model-based techniques to help guide the challenge of go-no-go decision making during drug development. In the example presented in the article, the team used a simulation platform to ascertain whether there would be any clinically relevant differences between 4 different paracetamol formulations. To complete the simulation, in-house PK data were combined with a previously published PD model for pain to “learn”<sup>18</sup> about the potential benefits of the technology. This was necessary because running a confirmatory clinical trial was prohibitively expensive for the company.

The results indicated that the formulation technology under investigation resulted in lower and earlier NNTB values compared with currently available formulations over a 45-minute interval post dose, supporting the decision that the technology could have a wider reaching impact for drugs where a rapid onset of action provides a clinical benefit (ie, analgesics, antihistamines, and hypnotics).

The model-based simulations not only supported the go-no-go decision but also provided information about design considerations for a confirmatory trial to verify the simulation results. Specifically, it was possible to identify target time points where differences in pain control between formulations were greater (ie, 10-20 minutes post dose). Similarly, it was possible to identify time points where negligible differences were evident and data collection could be avoided (ie, over the first 10 minutes and later than 45 minutes post dose).

The results presented are not without limitation, which must be considered when using such material to guide go-no-go decisions. Specifically, the simulation results are entirely constrained by the models

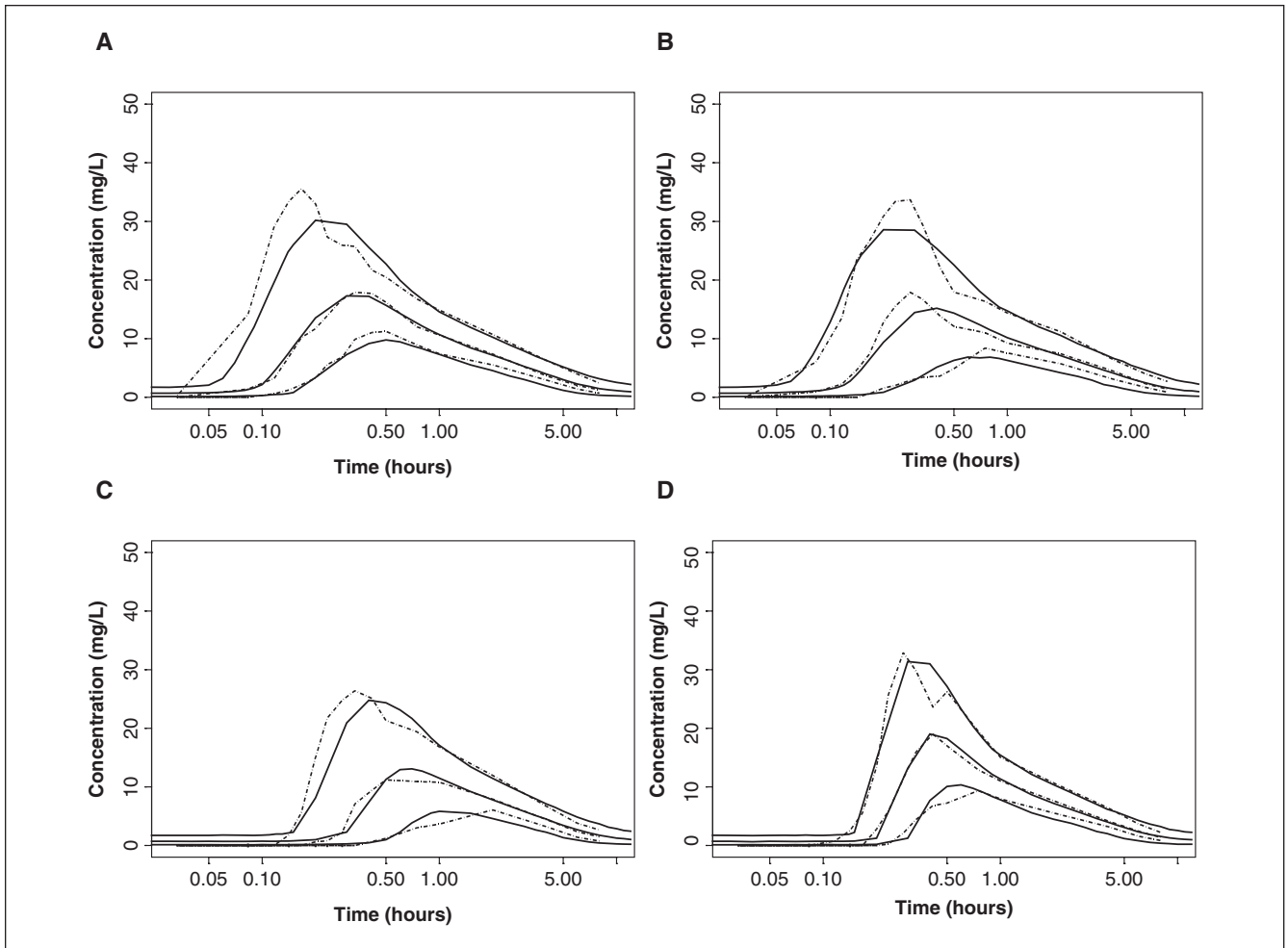


Figure 2. Visual predictive checks for (A) Imaginot A, (B) Imaginot B, (C) Tylenol, and (D) Panadol Rapid. The lower, middle, and upper solid lines represent the model's 10th, 50th, and 90th prediction intervals, whereas the lower, middle, and upper dotted lines represent the 10th, 50th, and 90th percentiles from the observed data.

**Table III** Pharmacokinetic Parameters for Paracetamol Formulations

Formulation	Parameter Values						
	CL/F, L/h	V <sub>c</sub> /F, L	R	V <sub>p</sub> /F, L	CL2/F, L/h	Ka, /h	TLAG, h
Imaginot A	21.3 (7.30)	19.6 (15.0)	0.310	43.2 (12.5)	69.1 (22.9)	4.61 (73.8)	0.0861 (25.0)
Imaginot B	21.7 (9.10)	19.9 (15.3)	0.362	43.9 (13.1)	70.3 (23.2)	3.80 (131)	0.101 (37.4)
Tylenol	21.0 (8.64)	19.3 (14.1)	0.310	42.6 (14.4)	68.1 (26.0)	2.85 (130)	0.271 (26.9)
Panadol Rapid	21.6 (6.92)	19.8 (13.5)	0.240	43.7 (12.0)	69.9 (21.9)	5.74 (81.0)	0.206 (7.36)

CL, apparent clearance; CL2, apparent intercompartmental clearance; Ka, absorption rate constant; R, correlation between clearance and central volume of distribution; TLAG, lag time; V<sub>c</sub>, apparent central volume of distribution; V<sub>p</sub>, apparent peripheral volume of distribution. Residual error: proportional, CCV = 6.4%; additive, SD = 1.05 mg/L. Parameter values represented as geometric mean, with between-subject variability (as percentage coefficient of variation) shown in parentheses.

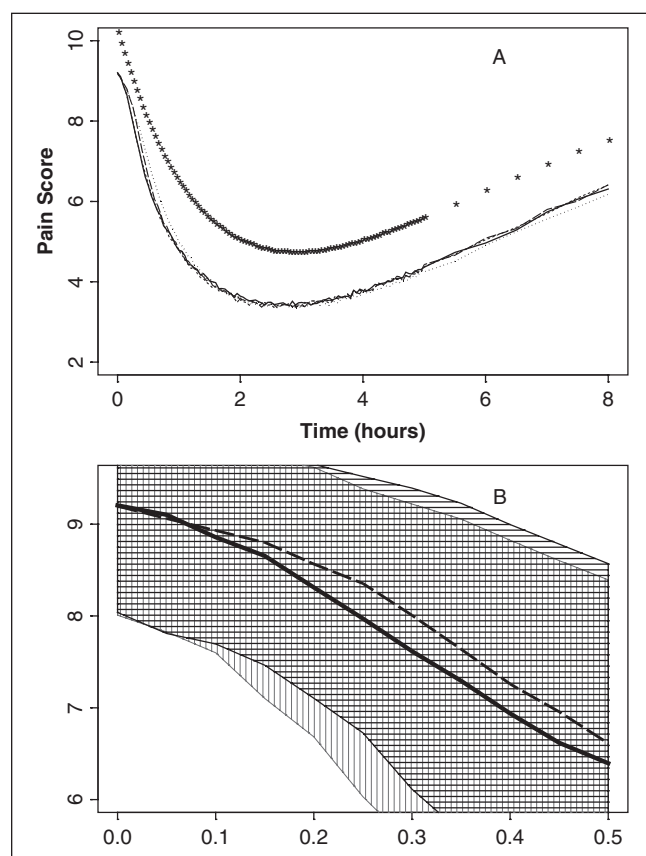


Figure 3. Model predicted pain scores over time: (A) 0 to 8 hours post dose and (B) 0 to 0.5 hours post dose. (A) The lines represent the 50th prediction interval, where \*\*\* represents the placebo response, — represents Imaginot A, ---- represents Imaginot B, ... represents Tylenol, and — — represents Panadol Rapid. (B) The vertical and horizontal lined areas represent the 90% prediction intervals for Imaginot A and Panadol, respectively. The hatched area therefore represents the overlap between the 2 compounds.

used to generate them. In this example, it is evident that the peak 90th prediction interval for Imaginot A and B is lower than the observed peak 90th percentile, with the peak 90th prediction interval for Imaginot A and Tylenol lagging behind the peak 90th percentiles. This could certainly bias results, although it would likely result in a conservative estimate of the NNTBs for these particular formulations rather than inflating any superiority. It is also worth noting that individual parameters were resampled from their distributions if the placebo or drug effects were not constrained between 0 and 1 and could impart some bias on the final results.

The PK models were built using data collected from young adults, whereas the PD model was developed from children post tonsillectomy.<sup>11</sup> When using model-based simulations to predict clinical trial outcomes, it is desirable to use PK and PD models developed using data from subjects in whom the prediction is being made. However, it is common to want to predict outside the population from which the model was developed, and careful evaluation of the models predictive properties must therefore be considered. In this example, the PK parameters were developed in healthy volunteers, and no consideration (ie, inclusion of covariates) was given to body size, concurrent disease states, and age, for example. As such, the predictions apply to normal weighted, otherwise healthy young adults. Similarly, the PD model was developed in pediatric subjects, which might not seem appropriate to use to predict pain in adults. However, it has been shown that analgesic data from adults are consistent with effect site concentration-response described in children,<sup>19</sup> with Panadol Rapid significantly decreasing pain compared with placebo at 15 minutes post dose when treating a sore throat in young

**Table IV** Number Needed to Treat Compared With Placebo to Benefit 1 Patient (NNTB) for 50% and 95% Pain Relief Over Various Time Intervals

	50% Pain Relief							95% Pain Relief
	10 min	15 min	30 min	45 min	1 h	2 h	4 h	8 h
Imaginot A	278 (161-1000)	31.6 (25.2-42.4)	3.97 (3.61-4.41)	2.75 (2.52-3.02)	3.33 (3.01-3.71)	14.3 (11.7-18.3)	48.1 (33.9-82.4)	8.83 (7.09-11.7)
Imaginot B	250 (149-775)	25.5 (20.9-32.6)	3.71 (3.39-4.11)	2.88 (2.64-3.18)	3.53 (3.26-3.86)	14.1 (12.1-16.9)	44.6 (32.2-72.8)	7.86 (6.44-10.1)
Tylenol	∞ (902 <sup>a</sup> to ∞ to 902)	313 (736 <sup>a</sup> to ∞ to 129)	9.33 (7.81-11.6)	4.31 (3.81-4.96)	4.19 (3.72-4.79)	13.9 (11.4-17.7)	44.6 (32.2-72.8)	7.89 (6.45-10.1)
Panadol Rapid	2500 (10 40 <sup>a</sup> to ∞ to 569)	208 (49 215 <sup>a</sup> to ∞ to 104)	5.73 (5.07-6.60)	3.20 (2.91-3.56)	3.62 (3.26-4.07)	13.9 (11.4-17.7)	42.4 (31.0-67.0)	8.45 (6.83-11.1)

Numbers represent NNTB, with values in parentheses representing the 95% confidence interval.

a. Number needed to treat to harm 1 patient (NNTH).

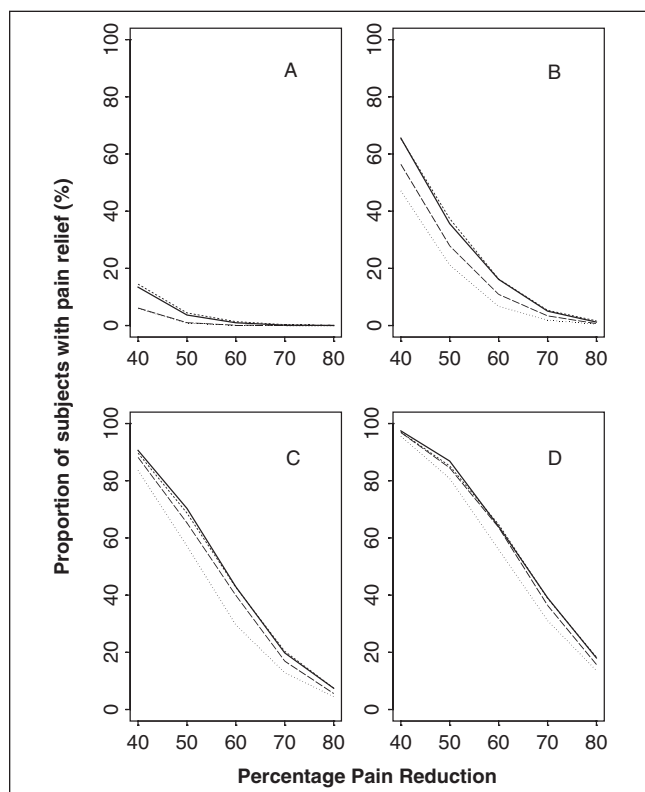


Figure 4. Proportion of subjects with varying degrees of pain relief at (A) 15 minutes, (B) 30 minutes, (C) 45 minutes, and (D) 60 minutes post dose. The lines represent the 50th prediction interval where -- represents Imaginot A, .... represents Imaginot B, -.- represents Tylenol, and — represents Panadol Rapid.

adults.<sup>20</sup> Both these results support the use of the pediatric PD model to predict adult pain scores. One final limitation of the PD model was that it lacked any dropout component,<sup>21</sup> potentially downwardly biasing the results due to the high dropout rates frequently seen in pain studies over the first few hours post dose.

## CONCLUSION

This model-based simulation study proved helpful in understanding potential differences in clinical outcome between 4 differing formulations of paracetamol. The analysis suggested that the formulation technology under investigation might provide a clinically significant reduction in the time to onset of pain relief from paracetamol. Confirmation in a randomized clinical trial is needed to account for the limitations of the simulation experiments.

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