Perioperative Pharmacodynamics of Acetaminophen Analgesia in Children


Background: There are no adequate pharmacodynamic data relating concentrations of acetaminophen in serum to analgesia.

Methods: Children undergoing outpatient tonsillectomy were administered acetaminophen either orally, 0.5–1.0 h preoperatively (n = 20), or per rectum at induction of anesthesia (n = 100). No other analgesic agents were administered. Individual concentrations of acetaminophen in serum and pain scores (0–10) measured over a 4-h postoperative period were analyzed using a nonlinear mixed-effects model (NONMEM).

Results: Mean (% CV) estimates of population pharmacokinetic parameters with percent coefficient of variation, standardized to a 70-kg person, for a one-compartment model with first-order input, lag time, and first order-elimination were a volume of distribution of 60 (21) l and a clearance of 13.5 (46) l/h. Rectally administered acetaminophen had an absorption half-life of 35 (63) min with a lag time of 40 min. The absorption half-life for the oral preparation was 4.5 (63) min without a detectable lag time. The relative bioavailability of the rectal compared with the oral formulation was 0.54. The equilibration half-time of an effect compartment was 1.6 (131) h. Pharmacodynamic population parameter estimates (percent coefficient of variation) for a fractional sigmoidal E_{max} model, in which the greatest possible pain relief equates to an E_{max} of 1, were E_{max} = 1, E_{0.5} (the concentration producing 50% of E_{max}) = 3.4 (94) mg/l, and Hill coefficient = 0.54 (42).

Conclusions: The pharmacodynamics of acetaminophen can be described using a sigmoidal E_{max} model with a low Hill coefficient. To achieve a mean post-tonsillectomy pain score of 3.6 of 10, an effect compartment concentration of 10 mg/l is necessary. (Key words: Allometric size model; anesthesia; paracetamol; pharmacokinetic–pharmacodynamic modeling.)

ACETAMINOPHEN is an antipyretic analgesic drug used widely in pediatric clinical practice. Concentrations of acetaminophen between 10 and 20 mg/l are known to produce an antipyretic effect.1 The analgesic effect of acetaminophen is thought to be related directly to its concentration,2 but no relation has been established between concentrations of acetaminophen and analgesia in humans.

We monitored children undergoing adenotonsillectomy to determine how concentration of acetaminophen is related to analgesia. A pharmacokinetic–pharmacodynamic model3 was used to describe the concentration–effect relationship.

Materials and Methods

Approval from the Regional Health Authority Ethics Committee was obtained. Parental consent was obtained for each child. Children with an American Society of Anesthesiologists physical status 1 or 2, aged 2–15 yr and scheduled for outpatient tonsillectomy with or without adenoidectomy, were enrolled in the study.

Children were not premedicated. Anesthesia was induced with either propofol (3 mg/kg, administered intravenously) or inhaled halothane and 70% nitrous oxide in oxygen. Atracurium (0.4 mg/kg) was administered intravenously to facilitate tracheal intubation. Anesthetic maintenance consisted of halothane in 70% nitrous oxide in oxygen with controlled ventilation. At the conclusion of the procedure, all children received neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg). Children were extubated after the surgical field was dry and after resumption of spontaneous respiration. They were then transported to the recovery room.
Tonsil dissection was performed using monopolar coagulation diathermy, and any subsequent bleeding was arrested with packing or bipolar diathermy. The average blood loss using this technique was 10-20 ml. All surgery was performed by one operator.

All children received 20 ml/kg of a balanced salt solution intravenously and metoclopramide (0.15 mg/kg) intraoperatively. Acetaminophen (≈ 40 mg/kg) was administered either between 0.5 and 1.0 h preoperatively as an oral elixir or per rectum after anesthetic induction. The rectal suppositories were an acetaminophen slurry contained in a glycolgelatin capsule and are available in two sizes: 125 and 250 mg (Sanofi Winthrop [NZ] Ltd., Auckland, New Zealand). The oral elixir was supplied as a sugar-free, alcohol-free preparation with a standard strength of 250 mg/5 ml (SmithKline Beecham [NZ] Ltd., Auckland, New Zealand).

Postoperative pain was assessed using a visual analog scale (0-10). A score of 10 represents the worst pain imaginable to the individual child. An observer-evaluated pain scale was used in those children younger than 5 yr old. Pain scores were recorded every half hour after admission to the recovery room until discharge from the day-stay facility, approximately 3 to 4 h after surgery. Blood samples for measurement of concentrations of acetaminophen were taken from indwelling venous cannulae. Three to five samples were taken from each patient at 30-min intervals, beginning approximately 30 min after admission to the recovery room in those children who were administered rectal suppositories. The group administered elixir had the first blood sample taken after anesthetic induction, and then samples were taken hourly for up to 7 h after the administration of acetaminophen. Pain score recordings and blood sampling were performed by a research nurse.

Children in severe pain (as assessed by recovery room nursing staff) had a pain score assessment, had a blood sample drawn for an acetaminophen assay, and were then administered rescue morphine (0.05 mg/kg) as needed. No further data were collected from this subgroup of children. Once awake and alert, all children were offered flavored blocks of ice. They were kept for a minimum of 4 h before discharge to home.

**Acetaminophen Assay**

Serum from each patient was separated by centrifugation and stored at −20°C until analysis. The concentration of acetaminophen was determined by fluorescence polarization immunoassay using the Abbott TDX (Abbott Laboratories, Abbott Park, IL) according to manufacturer instructions. The stored samples were analyzed in batches with three controls in each batch. The mean (SD) values obtained for the controls (supplied by Baxter Diagnostics, Deerfield, IL) were 55.9 (2.4), 30.2 (1.4), and 9.9 (0.6) mg/l. These are within the expected ranges quoted by the manufacturers. The between-batch precision values at these levels are 4.3, 5.2, and 6.1% respectively.

**Modeling**

**Pharmacokinetic and Link Models**

Modeling was performed using a nonlinear mixed-effects (NONMEM) model. The interindividual variability in model parameters was modeled by a proportional variance model. The covariance between clearance, volume of distribution, and absorption halftime was incorporated into the model. An additive term characterized the residual error. This error model assumes that the residual error is the same order of magnitude over the whole range of measurements. The population mean parameters, interindividual variance, and residual variance were estimated using the first-order conditional estimate method using ADVAN 4 TRANS 1 of NONMEM V.

A first-order input with a lag time, first-order elimination, one-compartment disposition model with delayed effects accounted for by an effect compartment was used. The ADVAN 4 subroutine describes a two-compartment disposition model. The model was parameterized in terms of the absorption half-life ($T_{\text{abs, min}}$), an absorption lag time ($T_{\text{lag, min}}$), the central compartment volume ($V/F_{\text{oral, l}}$), and the total body clearance ($CL/F_{\text{oral, l/h}}$) after oral administration. The first compartment of the pharmacokinetic model was used to predict concentrations in the central compartment (volume of distribution), and the second compartment was used to predict effect-compartment concentrations. This effect compartment was given a small volume by scaling the first-order rate constant for transfer from the central to the effect compartment to $\frac{1}{1000}$ of the elimination rate constant from the central compartment, so as not to influence the pharmacokinetics of the central compartment.

Acetaminophen was administered as an extravascular dose, and clearance and volume of distribution are confounded by bioavailability. Parameter estimates for $CL/F_{\text{oral}}$ and $V/F_{\text{oral}}$ are those determined for oral administration. $F_{\text{rectal/oral}}$ is the relative bioavailability of the
rectal compared with the oral formulation. Parameter estimates after rectal administration (CL/F\text{rectal}, V/F\text{rectal}) were determined by dividing oral parameter estimates by F\text{rectal/oral}.

The quality of fit of the pharmacokinetic model to data was judged by the NONMEM objective function and by visual examination of plots of observed versus predicted concentrations.

**Pharmacodynamic Model**

A fractional sigmoid $E_{\text{max}}$ model was

$$E = E_0 \cdot \left(1 - \frac{E_{\text{max}} \cdot C_e}{EC_{50} + C_e}\right)$$

(1)

where $E_0$ is the baseline response (fixed at 10, maximal pain), $E_{\text{max}}$ is the maximum pain reduction, $C_e$ (mg/l) is the concentration in the effect compartment, $EC_{50}$ (mg/l) is the concentration producing 50% $E_{\text{max}}$, and $S$ is the Hill coefficient.

The use of this fractional $E_{\text{max}}$ model implies a maximum effect of 1 (i.e., greatest possible pain relief). A constraint model was initially used to ensure an $E_{\text{max}}$ of 1 or less in each individual. After it was determined that the estimate of $E_{\text{max}}$ was close to 1, however, $E_{\text{max}}$ was fixed at 1 and the variability was set to zero (see appendix).

**Scaling for Size**

Many functional properties of the body, such as metabolic rate, have a nonlinear relationship to size. Children between 2 and 15 yr old have a large weight range. Consequently, parameter values were standardized for a body weight of 70 kg using an allometric power model:

$$P_i = P_{\text{std}} \cdot \left(\frac{W_i}{W_{\text{std}}}\right)^{PWR}$$

(2)

where $P_i$ is the parameter in the $i$th individual, $W_i$ is the weight in the $i$th individual, and $P_{\text{std}}$ is the parameter in an individual with a weight $W_{\text{std}}$. The PWR parameter was 0.75 for clearance, 1 for volumes of distribution, and 0.25 for equilibration half-time ($T_{eq}$). $T_{abs}$ was not standardized for size, because this parameter is formulation determined.

**Covariate Analysis**

The model-building process included the examination of bias in the two types of pain scale used and in the effects of age, weight, and gender covariates (see appendix). Improvement in the objective function was referred to the chi-squared distribution to assess significance.

Simulation Using Parameter Estimates

A pharmacokinetic-pharmacodynamic simulation was performed of a perioperative dose regimen of 40 mg/kg administered orally preoperatively, supplemented 2 h later by an intraoperative rectal dose of 20 mg/kg. Pharmacokinetic parameters of acetaminophen and their coefficients of variation were used to predict time-concentration profiles (Pharsight Trial Designer, Version 1; Pharsight Corporation, Palo Alto, CA) in 1,000 children (weights, 20–30 kg) using a one-compartment, first-order input, first-order elimination model. An additive measurement error of 1.5 mg/l was applied to concentrations of acetaminophen, with a minimal quantifiable concentration of 1.5 mg/l.

**Results**

One hundred twenty children were enrolled in the study. Mean (SD) age was 8.1 (3.6) yr and mean (SD) weight was 34 (17) kg. There were 52 boys and 68 girls. Twenty children were administered acetaminophen orally preoperatively, and 100 children were administered acetaminophen rectally intraoperatively. Seventeen children were administered rescue morphine intravenously (0.05 mg/kg) within the first 30 min after surgery, 15 from the suppository group and 2 from the group administered elixir. None of the remaining 103 children required further pain-relieving medication during the study period.

Complete sampling from all children was not possible because of patient or parent refusal, loss of intravenous access, venoconstriction, or early hospital discharge. A total of 907 data points (444 concentrations and 463 pain scores) were collected for analysis; 871 (425 concentrations and 466 pain scores) remained after exclusion of children who required rescue morphine.

Pharmacokinetic population estimates are shown in table 1. The repeat analysis without the 17 children administered rescue morphine gave similar parameter estimates. These pharmacokinetic parameter estimates are similar to those reported previously using the same model (table 1). The mean (SD) concentration of acetaminophen in serum at 30 min in the 15 children who were administered morphine in the suppository group was not different from the remaining children (9.8 [5.7] vs. 8.3 [4.0] mg/l; $t$ test, $P = 0.19$). The individual post boe ETA (rounded effects in the residual errors, see appendix) values for the structural parameters CL/Foral, V/Foral, and $T_{abs}$ for these patients were not different.

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from the remaining patients (t test, \( P = 0.93, 0.99, \) and 0.83, respectively).

Pharmacodynamic population estimates are shown in table 2. Parameter estimates were unchanged when those children administered rescue morphine were excluded, with the exception of a shorter \( T_{eq} (1.3 \text{ h}) \), percent coefficient of variation \( [CV\%] = 100\% \times 1.6 \text{ h}, CV\% = 131\% \). The mean \( T_{eq} \) of the children administered rescue morphine was longer than those not administered rescue morphine (1.5 h, CV\% = 100\% \times 2.4 \text{ h}, CV\% = 74\%; t test, \( P = 0.002 \)). The covariance between clearance, distribution volume, and absorption half-time is shown in table 3.

Time-concentration profiles for each individual, mean of the observations, and the mean predicted profile are shown in figure 1. Pharmacodynamic data are shown in figure 2. The relation between effect-compartment concentration and pain score is shown in figure 3. Effect-compartment concentrations of 10–20 mg/L, which have been proposed to reduce fever, \(^1\) were associated with pain scores of 3.6–2.8 of 10. Figures 4 and 5 show the quality of fit for pharmacokinetic and pharmacodynamic, respectively.

A scaling parameter applied to the \( E_{max} \) or \( EC_{50} \) in children younger than 5 yr who had pain measured by an observer-dependent pain score did not significantly improve the objective function (objective function change = 0.5).

Figure 6 shows changes in CL/Foral with age. Individual clearance estimates increased with age when no correction was made for size. When these estimates were standardized to a 70-kg person using an allometric power model, there was no additional relation with age (objective function change = 3.5). Figure 7 shows the relation between V/Foral and age. After volume of distribution was corrected for size using an allometric model with an exponential of 1, there was also no additional relation with age (objective function change = 1.4). There was no correlation between gender and pharmacokinetic or pharmacodynamic parameters.

Figure 8 shows the predicted median time-concentration profile obtained from the simulation. A preoperative oral dose of 40 mg/kg was followed by an intraoperative rectal dose of 20 mg/kg 2 h later. Concentrations higher than 10 mg/L and higher than 20 mg/L at 6 h were achieved in 78.4% and 50.2% of children, respectively. The addition of a supplemental rectal dose intraoperatively resulted in concentrations higher than 10 mg/L for 2.5 h longer than a single 40-mg/kg dose administered preoperatively.

### Discussion

There are no adequate data concerning the concentration-antalgic effect relation of acetaminophen in humans. Analgesia in children undergoing tonsillectomy has been described using acetaminophen (40 mg/kg) administered orally preoperatively. \(^1^2\) In that study, delayed effects were not accounted for. Analysis of those
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Fig. 1. Time–concentration profiles for each patient, with the mean of the observations shown as a solid line. The mean predicted profile is shown as a dashed line. (A) Data from children administered suppositories. (B) Data from children administered elixir.

Data suggested that 50% of children had satisfactory analgesia at a concentration in serum of 17 mg/l.13 We would expect equivalent effect-compartment concentrations to be lower because of delayed onset of effects.

The current article describes a pharmacokinetic-pharmacodynamic relationship for analgesia of acetaminophen in which the fractional $E_{\text{max}}$ (the asymptomatic effect for the $E_{\text{max}}$ model) estimate is 1 (i.e., greatest possible pain relief). Doses required to approach $E_{\text{max}}$ and achieve full pain relief are not administered because of the inherent dangers of hepatotoxicity. There are few data concerning efficacy of simple analgesic agents. An $E_{\text{max}}$ value of 3.45 (pain scale, 0–4) has been described for the nonsteroidal antiinflammatory agent ketorolac in adults after orthopedic surgery.14 The analgesic response seen, however, may depend on the magnitude of the pain. $E_{\text{max}}$ is a measure of drug effect and not pain magnitude. Acetaminophen may not be able to relieve pain of greater magnitude because of other types of surgical trauma.

The pain associated with noxious stimuli varies from patient to patient. An interindividual variability of three- to fivefold has been described for the concentration of opioid in plasma that blocks a defined response to a
stimulus in 50% of patients.\textsuperscript{15,16,17} We estimate a CV% of 94% for the EC\textsubscript{50}. The imprecision and bias in the EC\textsubscript{50} and E\textsubscript{max} parameter estimates, however, are influenced by our inability to measure an effect intensity more than 75% of E\textsubscript{max}. Dutta \textit{et al}.\textsuperscript{18} showed that this imprecision is magnified when the Hill coefficient is smaller, as is the case in the current study. Further work is necessary to delineate the EC\textsubscript{50} with confidence.

A pharmacodynamic concentration-temperature reduction model for fever for acetaminophen has been described in children.\textsuperscript{19} The shape of that curve is much steeper in its central portion (Hill coefficient = 2.65) than the curve describing analgesia (Hill coefficient = 0.54). Doubling the analgesic target concentration from 10 to 20 mg/l only decreases the pain score by less than 1, and the consequences of constant exposure to this higher concentration are unknown.

Acetaminophen has a direct action on the central nervous system.\textsuperscript{20} Concentrations of acetaminophen in the cerebral spinal fluid peaked 2 h after intravenous administration of an acetaminophen prodrug (propacetamol) in a study by Bannwarth \textit{et al}.\textsuperscript{21} in adult patients with rheumatic and nerve root compression pain. This cerebrospinal fluid time-concentration profile was similar to the time delay between concentrations of acetaminophen and analgesic effect reported in adult volunteers.\textsuperscript{22,23} We reported a half-time estimate of 2.1 h for equilibration between serum and cerebrospinal fluid using the pooled data from Bannwarth \textit{et al}.\textsuperscript{19} A delayed effect has been described relating temperature reduction to concentrations of acetaminophen in plasma in febrile children with a T\textsubscript{eq} value of 0.99 h.\textsuperscript{19,24} The T\textsubscript{eq} estimate of 1.6 h for acetaminophen analgesia is similar to these estimates.

An observer-dependent pain scale was used in children.
Fig. 4. Quality of fit of pharmacokinetic data. The Y axis of each panel displays the ratio of measured concentrations to those predicted from pharmacokinetic analysis. (A) Values from the population parameters. (B) Values from the NONMEM/post hoc step based on values of the parameters for the specific individual.

younger than 5 yr old. Validation of this observer-dependent pain scale against a standard scoring system has been made by using Pearson correlation (r = 0.9),25 although precision and bias have not been estimated. Although the correlation is high, this scale may over- or underpredict.


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There are no longitudinal studies comparing this observer-dependent pain scale used in children younger than 5 yr old with the standard visual analog self-scoring system used in older children and adults. We had concerns that the observer-dependent pain scale may have bias compared with the self-scoring system, but there was no improvement in the objective function when a scaling parameter to account for such a difference was introduced.

Analysis of the pharmacokinetic–pharmacodynamic rela-
Fig. 5. Quality of fit of pharmacodynamic data. The Y axis of each panel displays the difference between measured pain scores with those predicted from modeling. (A) Values from the population parameters. (B) Values from NONMEM’s post hoc step based on values of the parameters for the specific individual.

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![Fig. 6. Relation of clearance (CL/Foral) estimates to age. Individual CL/Foral estimates (open diamonds; l/h) increase with age when no correction is made for size. When these estimates are standardized to a 70-kg person using an allometric 3/4 power model (filled squares; l/h per 70 kg body weight), there is no influence of age on the prediction of CL/Foral.](image)

The population pharmacodynamic model used in our study has three potential drawbacks. First, placebo effect was not accounted for, and it can contribute significant analgesia. We found that 24% of children received adequate analgesia after tonsillectomy, despite no detectable acetaminophen in plasma in a previous study. The continuing use of placebo as a control, however, has been strongly argued against in the literature and was not used in this study. Second, pain intensity was assumed to be constant over the 3-h postoperative period. Posttonsillectomy pain resolves over days, not hours. The 20 children administered acetaminophen orally preoperatively probably required further pain-relieving medication at approximately 6–8 h because of a return of pain. This trend can be seen in figure 2. It would seem reasonable to assume that the pain was constant over the study period. Finally, the baseline response (E0) was fixed at 10. The pharmacodynamic model allowed Emax to be different from 1, but the estimate from the data was 1. It was the children themselves who rated their pain in a way that led to the conclusion that Emax was 1. The pain score in the absence of drug would have been 10 of 10.

![Fig. 7. Relation of volume of distribution (V/Foral) estimates to age. Individual V/Foral estimates (open diamonds; l) increase with age when no correction is made for size. When these estimates are standardized to a 70-kg person using an allometric 3/4 power model (filled squares; l/70 kg body weight), there is no influence of age on the prediction of V/Foral.](image)

Patients who received rescue medication and who were withdrawn from the study may introduce additional bias, because the remaining study patients are those who do not have such severe pain; the reason for their reduced analgesia may not be solely pharmacological. Dropouts in the current study, however, occurred before the drug could have effect or before they could contribute any reasonable amount of data. Sheiner excluded patients who dropped out before 1 h in an analysis of analgesia with bromfenac. Results of the data analysis with these early dropouts included or excluded in our study were essentially the same, with the exception of the equilibration half-time. It is possible that these children dropped out because the onset of effect was markedly delayed. Including these children avoids some of the bias that would result from deleting the data from those individuals entirely.

![Fig. 8. Simulation of administration of acetaminophen. A loading dose of 40 mg/kg administered orally preoperatively, supplemented by a 20-mg/kg suppository 2 h later. Parameter estimates, standardized to a 70-kg person, are V/Foral = 60 l/70 kg, CL/Foral = 13.5 l•h⁻¹•70 kg⁻¹, and T1/2 = 4.5 min for the oral elixir and T1/2 = 35 min with a lag time of 40 min for the suppository. The Foral value was 0.54. Variability is shown using box-and-whisker plots. The central box represents the fiftieth percentile. Indentations in this box indicate the median. Values outside the 97.5% percentile are shown individually.](image)
Pain scores were treated as continuous rather than as categoric data. Pain was measured using an 11-point pain scale, which ranged from no pain (0.10) to the worst imaginable (0 of 10). This pain scale differs from the 5-point (0–4) pain scale used to describe analgesia with ketorolac14 and bromfenac15 using a categoric pharmacodynamic model. Because of the larger number of points in the pain scale used in our study, it seems reasonable to analyze the data as continuous rather than as categoric.

The pharmacokinetic model used a first-order input model with a lag time to describe absorption. Birmingham et al.27 reported a first-order input model with a zero-order dissolution time to describe absorption characteristics of acetaminophen suppositories. This model was impractical in our study, because we had no pharmacokinetic data for the first hour after rectal administration. In addition, the suppositories used in our study were glycolatin capsules containing an acetaminophen slurry. The slurry is released rapidly once the capsule wall is breached, and consequently a lag-time absorption model may have greater physiologic relevance, although this was not investigated.

The allometric 3/4 power model may be a more accurate predictor of size than the per-kilogram model for metabolic processes.8,10 In humans, under-prediction of clearance by more than 10% occurs at body weights less than 47 kg when the per-kilogram model is used.8 The use of the per-kilogram model in young children has led to the misconception that children have an enhanced capacity to metabolize drugs because of their relatively large liver size or increased hepatic blood flow.26,29 The allometric pharmacokinetic model has been used with success for cross-species scaling in pharmacokinetics.30,31 Figure 6 shows that individual clearance estimates increase with age. When these estimates were standardized to a 70-kg human using the allometric 3/4 power model, we were unable to demonstrate age-related changes.

We simulated a time-concentration profile for children (20–50 kg) using a perioperative dose regimen of 40 mg/kg administered orally plus 20 mg/kg per rectum 2 h later (fig. 8). Pain scores of less than 4 of 10, which are described as satisfactory in children,6 are achieved at a concentration of 10 mg/l. We believe a target concentration of 10 mg/l will provide satisfactory analgesia for 50% of children undergoing surgery similar to tonsillectomies. If admission to the recovery room occurs 2–4 h after administration, then a concentration higher than 20 mg/l (and a mean pain score of 2.8 of 10) is achieved in most children. We predict that half of the simulated children will have satisfactory analgesia 8 h after administration. The addition of the supplemental rectal dose intraoperatively resulted in concentrations higher than 10 mg/l for 2.5 h longer than a single 40-mg/kg dose administered preoperatively.

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References


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Appendix

Constraint Model for Emax
THETA is the typical population value for Emax, and EXP(ETA) expresses the proportional random difference between this parameter of the ith subject and the population mean parameter. Values of ETA are assumed to be identically normally distributed with a mean of 0 and diagonal variance-covariance matrix OMEGA with diagonal elements (EPSILON_+^2). The log-normal distribution of parameters is a common assumption in pharmacokinetic and pharmacodynamic modeling because it prevents the parameters from having nonphysiologic negative values and because the distribution of parameters tends to be skewed.

Emax was constrained to be between 0 and 1 for individuals.

\[ \text{TMP} = \exp[\log(\text{THETA}/(1 + \text{THETA} + \text{ETA})] \] (5)

\[ \text{EMAX} = \text{TMP}/(1 + \text{TMP}) \] (4)

At the extreme THETA of 1, there can be no interindividual variability about Emax; the CV approaches 0.

Covariate Analysis

Pain Scale. An observer-dependent pain scale was used in children younger than 5 yr old, whereas a visual analog scoring system was used in older children. A scaling parameter was applied to Emax and EC50 in those children 5 yr old or younger.

IF (AGE.LE.5) THEN
   FAGE = THETA
   ELSE
   FAGE = 1
ENDIF (5)

This factor for age (FAGE) is then applied to Emax or EC50. For example,

\[ E = E0*(1 - (\text{FAGE}^*E_{\text{max}}^*\text{Ce}^*)(\text{EC}_{50}^N + \text{Ce}^N)) \] (6)

Gender. Gender was investigated using a similar code.

Age. The effects of a THETA value for increasing age on Emax, EC50, Cl, and V were investigated. This THETA was applied to these parameters independently.

IF (AGE.LE.0) THEN
   FAGE = 1
   ELSE
   FAGE = THETA^AGE + 1
ENDIF (7)

This factor for age (FAGE) is then applied to the pharmacokinetic parameter estimate (e.g., EC50).

\[ E = E0*(1 - (\text{FAGE}^*E_{\text{max}}^*\text{Ce}^*)(\text{FAGE}^*\text{EC}_{50}^N + \text{Ce}^N)) \] (8)

The estimate for FAGE was 0.001 when applied to EC50, Emax, and V. None of the covariate analyses improved the objective function significantly.