

Acetaminophen Developmental Pharmacokinetics in Premature Neonates and Infants

A Pooled Population Analysis

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Background: The aim of this study was to describe acetaminophen developmental pharmacokinetics in premature neonates through infancy to suggest age-appropriate dosing regimens.

Methods: A population pharmacokinetic analysis of acetaminophen time-concentration profiles in 283 children (124 aged ≤ 6 months) reported in six studies was undertaken using nonlinear mixed-effects models. Neonates and infants were given either single or multiple doses of four different formulations: oral elixir, rectal solution, or triglyceride or capsular suppository. The median postnatal age of children younger than 6 months was 1 day (range, birth to 6 months), median postconception age was 40 weeks (range, 28-64 weeks), and median weight was 3.1 kg (range, 1.2-9.0 kg).

Results: Population pharmacokinetic parameter estimates and their variability (percent) for a one-compartment model with first-order input, lag time, and first-order elimination were as follows: volume of distribution, 66.6 l (20%); clearance, 12.5 l/h (44%); standardized to a 70-kg person using allometric " $1/4$ power" models. The volume of distribution decreased exponentially with a maturation half-life of 11.5 weeks from 109.7 l/70 kg at 28 weeks after conception to 72.9 l/70 kg by 60 weeks. Clearance increased from 28 weeks after conception ($0.74 \text{ l} \cdot \text{h}^{-1} \cdot 70 \text{ kg}^{-1}$) with a maturation half-life of 11.3 weeks to reach $10.8 \text{ l} \cdot \text{h}^{-1} \cdot 70 \text{ kg}^{-1}$ by 60 weeks. The absorption half-life for the oral elixir preparation was 0.21 h (120%) with a lag time of 0.42 h (70%), but absorption was further delayed (2 h) in premature neonates in the first few days of life. Absorption half-life parameters for the triglyceride base and capsule suppositories were 0.80 h (100%) and 1.4 h (57%), respectively. The absorption half-life for the rectal solution was 0.33 h. Absorption lag time was negligible by the rectal route for all three formulations. The bioavailability of the capsule suppository relative to elixir decreased with age from 0.92 (22%) at 28 weeks after conception to 0.86 at 2 yr of age, whereas the triglyceride base decreased from 0.86 (35%) at 28 weeks postconception to 0.5 at 2 yr of age. The relative bioavailability of the rectal solution was 0.66.

Conclusions: A mean steady state target concentration greater than 10 mg/l at trough can be achieved by an oral dose of $25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in premature neonates at 30 weeks' postconception, $45 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ at 34 weeks' gestation, $60 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ at term, and $90 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ at 6 months of age. The relative rectal bioavailability is formulation dependent and decreases with age. Similar concentrations can be achieved with maintenance rectal doses of 25 (capsule suppository) or 30 (triglyceride suppository) $\text{mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in premature neonates at 30 weeks' gestation, increasing to 90 (capsule suppository) or 120 (triglyceride suppository) $\text{mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ at 6 months. These regimens may cause hepatotoxicity in some individuals if used for longer than 2-3 days.

THERE are few data describing acetaminophen (paracetamol) pharmacokinetic parameters in premature neonates.^{1,2} The maximum concentration and the time at which this concentration is reached are commonly used to describe the time-concentration profile after administration of a drug. However, these values depend very much on when samples were taken. Knowledge of the population pharmacokinetic parameters (volume of distribution, total body clearance, and absorption half-life) allows the time-concentration profile for a typical individual to be predicted and, consequently, the dose for that individual to be predicted. The current paucity of information in this area is reflected in clinical practice. A recent survey of acetaminophen-prescribing habits in a children's hospital³ revealed that 50% of practitioners either did not know safe doses or did not prescribe acetaminophen during a patient's first 2 weeks of life. In the current study we pooled data from six published acetaminophen pharmacokinetic investigations in premature neonates, term neonates, and infants^{1,2,4-7} in an attempt to describe population-based developmental pharmacokinetics over the first few months of life and to propose dosing regimens that achieve a target concentration⁸ of 10 mg/l in this subpopulation.

The first year of life is a period of rapid growth and development. The enzyme processes responsible for drug clearance are developing, and body composition is changing to assume adult proportions. Acetaminophen clearance increases from birth in term neonates with a maturation half-life of 3.25 months to reach rates similar to adults by 12 months,⁵ but developmental pharmacokinetics in premature neonates are unknown. Developmental changes can be predicted by age and are independent of size, which is predicted by weight. Size is commonly standardized using either the per-kilogram or

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the body-surface-area methods. However, a great many physiologic-, structural-, and time-related variables scale predictably within and between species with weight exponents of 0.75, 1, and 0.25, respectively.⁹⁻¹¹ We used these "¼ power models" in the current analysis to disentangle size-related factors from age-related factors.

Materials and Methods

The authors of six published studies of acetaminophen pharmacokinetics in neonates and infants (age < 6 months) were asked to contribute their original data for a pooled population analysis. The Ethics Committee-Human Studies Committee at each of the five institutions approved individual study protocols, and parental consent was obtained for each child in all studies.

Study 1

van Lingen *et al.*² studied premature neonates (n = 28) given a 20-mg/kg rectal triglyceride suppository (a synthetic mixture of monoglycerides, diglycerides, and triglycerides of the saturated fatty acids C10-C18, prepared in house) within the first 2 days of birth. Subsequently, samples (0.1 ml) were taken from heparinized arterial and venous catheters at 30, 60, and 120 min, and 4, 6, 8, and 12 h. Data was included for two further subjects who were not included in the published article by van Lingen *et al.*² because of missing data from time-concentration profiles. However, such data lends itself to population analyses; therefore, 30 neonates were available for analysis. These premature neonates had a mean postconception age of 30.9 weeks (SD, 1.7; range, 28-34 weeks) and a mean weight of 1.37 kg (SD, 0.34; range, 0.75-1.95 kg). Acetaminophen assay was performed using a modified high-performance liquid chromatography method.¹²

Study 2

van Lingen *et al.*⁴ studied term neonates (n = 10) admitted to a neonatal intensive care unit after traumatic delivery. These neonates were given sequential 20-mg/kg rectal acetaminophen suppositories every 6 h for four doses in an effort to alleviate pain. Blood samples (0.2 ml) for acetaminophen assay were taken at 30, 60, and 90 min, and 3, 9, 15, 21, 24, and 27 h after the first dose had been given. Suppository formulation and assay method were the same as for study 1. The mean postconception age was 39.3 weeks (SD, 2.4; range, 36-42 weeks), and the mean weight was 3.54 kg (SD, 0.77; range, 2.68-4.81 kg)

Study 3

Lin *et al.*¹ gave premature neonates (n = 5) 20 mg/kg rectal acetaminophen contained in a 5% aqueous solution (1:1 dilution with sterile water of 10% Tylenol

Drops; McNeil Consumer Products Co., Fort Washington, PA). Serial 0.3-ml arterial blood samples were drawn *via* the umbilical artery catheter at 15, 30, 60, 120, and 240 min. Acetaminophen concentration was determined by fluorescence polarization immunoassay using the Abbott TDx (Abbott Laboratories, Toronto, Canada). These premature neonates had a mean postconception age of 33 weeks (SD, 1.6; range, 31-35 weeks), a mean postnatal age of 1.6 days (range, 1-4 days), and a mean weight of 2.02 kg (SD, 0.71; range, 1.5-2.8 kg)

Study 4

Anderson *et al.*⁵ randomized neonates and infants (n = 30) to sequentially receive one of three acetaminophen formulations (dose range, 30-40 mg/kg) over a 2-day period. These subjects had a mean postconception age of 38 weeks (SD, 2.3; range, 31-40 weeks) and a mean weight at the time of study of 3.5 kg (SD, 0.9; range, 2.5-6.8 kg). Sixteen were in their first 4 days of life, and in the remainder, postnatal age ranged from 2 weeks to 3 months. The formulations were oral elixir administered through a nasogastric feeding tube, triglyceride base suppository, and glycolgelatin capsule suppository. The oral elixir was supplied as a sugar-free, alcohol-free preparation with a standard strength of 250 mg/5 ml (Wellcome Pharmaceuticals, Auckland, New Zealand). The suppositories were an acetaminophen slurry (125 mg) contained in a glycolgelatin capsule (Winthrop, Sterling Pharmaceuticals NZ Ltd., Auckland, New Zealand), and the triglyceride base contained suspended acetaminophen in a bullet-shaped mold (25- and 50-mg doses, prepared in house). Nasogastric acetaminophen was given 1 h before enteral feeding in those neonates receiving food.

Arterial blood samples were taken from heparinized arterial cannulae. Approximately six samples over 10-16 h were taken after each dose. Blood samples (0.3 ml) were taken hourly for the first 4 h after acetaminophen administration, and then every 2-4 h. The total amount of blood drawn was limited to 5 ml. Acetaminophen concentration was determined by fluorescence polarization immunoassay using the Abbott TDx (Abbott Laboratories, Abbott Park, IL).

The data from Anderson *et al.*⁵ also included 150 older children (mean age, 95 months [SD, 46]; mean weight, 32 kg [SD 17]) given acetaminophen either as a capsule suppository or in the elixir formulation. This cohort was also used in the pooled population analysis to provide a baseline with which to compare neonatal pharmacokinetic parameters.

Study 5

Hopkins *et al.*⁶ reported time-concentration profiles in 28 febrile neonates, infants, and children after cardiac surgery (n = 41) given 15 mg/kg rectally. If bowel sounds were present, these patients were given an additional dose by nasogastric tube the following day. The

investigators were unable to retrieve their original data, but observations were taken from time-concentration profiles in figures 1-6 of their article. Samples (0.5 ml) were taken from heparinized arterial lines at 30, 60, 90, and 120 min, and 3, 4, 5, 6, and 8 h. Mean age, weight, and dose were obtained from table 1 in their original article. Postnatal age ranged from 6.9 days to 4.6 yr, and weight ranged from 2.6 to 13.6 kg. Infants and neonates were separated into four groups: neonates given suppository (age, 6.9-16.7 days; weight, 3.1-4.3 kg), neonates given elixir (age, 7.3-17.3 days; weight, 2.6-4.0 kg), infants given suppository (age, 2.3-4.9 months; weight, 3.0-5.4 kg), and infants given elixir (age, 2.4-6 months; weight, 2.6-6.0 kg). An infant suspension of 120 mg/5 ml (Calmic Medical Division, The Wellcome Foundation, London, United Kingdom) was used as elixir, and suppositories were triglyceride based (Suppocire; Gattefosse Ltd., Binfield, United Kingdom). Serum acetaminophen concentrations were determined using the Abbott Tdx fluorescence polarization immunoassay (Abbott Laboratories).

Study 6

Hansen *et al.*⁷ reported time-concentration profiles in 17 neonates and infants aged 160 postnatal days or younger. The mean postnatal age at the time of study was 71.5 days (SD, 47), the mean postconception age was 39.8 weeks (SD, 3.7), and the mean weight was 3.9 kg (SD, 1.4). Eight subjects were born prematurely. The mean postconception age at birth was 32.6 weeks. One 25-mg/kg rectal acetaminophen suppository was given perioperatively, and blood samples (0.7-1.0 ml) were drawn at 60, 120, 180, 240, 300, and 360 min. The acetaminophen was formulated in a triglyceride stearate base (Alvedon; Novex Pharma Ltd., Marlow, United Kingdom) and used in a strength of either 60 or 125 mg. Serum acetaminophen concentrations were measured by a colorimetric assay (Ectachem Clinical Chemistry Slides; Johnson & Johnson Clinical Diagnostics, Inc., New York, NY).

Pharmacokinetic Modeling

The pharmacokinetic model used in this analysis has been previously described.⁵ A first-order input with a lag time, first-order elimination, one-compartment disposition model was used to describe the time course of serum concentrations. The model was parameterized in terms of the absorption half-life (hours), absorption lag time (hours), apparent volume of distribution (liters), and total body clearance (l/h) after oral administration.

Acetaminophen was administered as an extravascular dose, and both clearance and distribution volume are confounded by bioavailability.

Population Parameter Estimations. Population parameter estimates were obtained using a nonlinear mixed effects model (NONMEM).¹³ This model accounts

for population parameter variability (between and within subjects) and residual variability (random effects), as well as parameter differences predicted by covariates (fixed effects). The population parameter variability in model parameters was modeled by a proportional variance model. An additive term characterized the residual unknown variability. This error model assumes that the residual variability is the same order of magnitude over the whole range of measurements. The population mean parameters, between subject variance and residual variance, were estimated using the first-order conditional estimate method using ADVAN 2 TRANS 2 of NONMEM V. Convergence criterion was three significant digits. A fortran F77 compiler (Watcom version 10.6, Sybase Inc., Chico, CA) was used with an Intel Celeron 333 MHz CPU (Intel Corp., Santa Clara, CA) under MS Windows 98 (Microsoft Corp., Seattle, WA).

The population parameter variability is modeled in terms of random effect (η) variables. Each of these variables is assumed to have mean 0 and a variance denoted by ω^2 , which is estimated. Population parameter variability for clearance and volume was partitioned into between-subject variability and between-occasion variability because neonates received paracetamol on up to four different occasions.

The covariance between two elements of η (e.g., clearance [CL] and volume of distribution [V]) is a measure of statistical association between these two variables. Their covariance is related to their correlation (R) *i.e.*,

$$R = \text{covariance}_{CL,V} / \sqrt{(\omega_{CL}^2 \times \omega_V^2)}$$

The covariance of clearance and distribution volume variability was incorporated into the model. This covariance is effected by factors that alter both clearance and volume together (e.g., protein binding, total body water), but variability of bioavailability is thought to be the major factor. Both between-subject and between-occasion covariance of clearance and volume was estimated.

In addition, there were six sources of data for the pooled population analysis. This between-study variability was accounted for by giving each investigator's study a separate residual error.

Covariate Analysis. The parameter values were standardized for a body weight of 70 kg using an allometric model.¹⁴

$$P_i = P_{std} \times (W_i/W_{std})^{PWR}$$

where P_i is the parameter in the *i*th individual, W_i is the weight in the *i*th individual, and P_{std} is the parameter in an individual with a weight W_{std} of 70 kg. The PWR exponent was 0.75 for clearance and 1 for distribution volumes.^{9,10,15,16}

The quality of fit of the pharmacokinetic model to the data was sought with the objective function of

Table 1. Standardized Population Pharmacokinetic Parameter Estimates

Parameter		Estimate	%CV
V_{std} (l/70 kg)		66.6	BSV 20 BOV 8
CL_{std} (l · h ⁻¹ · 70 kg ⁻¹)		12.5	BSV 44 BOV 39
Felixir		1 fixed	—
Tabs elixir (h)		0.214	120
Tlag elixir (h)		0.418	70
Rectal/oral	Triglyceride base (28 weeks PCAGE)	0.858	35
Tabs	Triglyceride base (h)	0.791	100
Tlag	Triglyceride base (h)	0.101	70
Rectal/oral	Capsule (28 weeks PCAGE)	0.919	22
Tabs	Capsule (h)	1.38	57
Tlag	Capsule (h)	0.149	70
Rectal/oral	Rectal solution	0.658	—
Tabs	Rectal solution (h)	0.326	68

%CV is the coefficient of variation for the population parameter estimate, except for V_{std} and CL_{std} , where between subject (BSV) and between occasion variability (BOV) were estimated.

CL_{std} = population estimate for CL/Foral; CL/Foral = clearance after oral administration (l · h⁻¹ · 70 kg⁻¹); V_{std} = population estimate for V/Foral; V/Foral = volume of distribution (l/70 kg); Tabs = absorption half-life after nasogastric (elixir) in children out of the neonatal period; triglyceride base suppository and capsule suppository administration (h); Tlag = absorption lag time after nasogastric (elixir), triglyceride base suppository and capsule suppository administration (h); Rectal/oral = relative bioavailability of the rectal compared to the oral formulation at 28 weeks postconception age (PCAGE).

NONMEM and by visual examination of plots of observed *versus* predicted concentrations. Models were nested, and an improvement in the objective function was referred to the chi-square distribution to assess significance, e.g., an objective function change of 3.84 is significant at $\alpha = 0.05$.

Covariate analysis included a model investigating age-related changes for clearance and volume of distribution:

$$V/Foral = (V_{std} \times (Wt/70)) \times (1 + \beta vol) \times \text{EXP}(-(\text{PCAGE}-28) \times \text{Ln}(2)/Tvol) \text{ l}$$

$$CL/Foral = (CL_{std} \times (Wt/70)^{0.75}) \times (1 + \beta cl) \times \text{EXP}(-(\text{PCAGE}-28) \times \text{Ln}(2)/Tcl) \text{ l/h}$$

where V_{std} and CL_{std} are the population estimates for apparent volume of distribution and total body clearance, respectively, standardized to a 70-kg person using allometric models; PCAGE is the postconception age in weeks; βvol and βcl are parameters estimating the fractional difference from V_{std} and CL_{std} at PCAGE weeks; and Tvol and Tcl describe the maturation half-lives of the age-related changes of apparent volume of distribution and total body clearance. The effect of postnatal age (PNAGE) was also investigated on absorption half-life:

$$\begin{aligned} \text{Tabs elixir (neonate)} &= \text{Tabs elixir (child)} \\ &\times (1 + \beta abs \times \text{EXP}(-\text{PNAGE in days}) \\ &\quad \times \text{Ln}(2)/\text{Telix})) \text{ h} \end{aligned}$$

where βabs is a parameter estimating the fraction above absorption half-life at birth and Telix describes the maturation half-life of the postnatal age-related change in oral absorption in days.

The relative bioavailability changes of the capsule and triglyceride base suppository formulations with increasing postconception age were explored as follows:

$$\begin{aligned} \text{Rectal/oral} &= \text{Rectal/oral at 28 weeks PCAGE} \\ &\quad \times \text{EXP}([\text{PCAGE}-28] * \text{slope}) \end{aligned}$$

where slope is a parameter describing the change of relative bioavailability over time (postconception age) for either the capsule or triglyceride base suppository formulation.

Results

The pooled analysis comprised 283 subjects (2,039 observations) and included 124 subjects aged 6 months or less. The median postnatal age of this subgroup was 1 day (range, birth to 6 months), median postconception age was 40 weeks (range, 28–64 weeks), and median weight was 3.1 kg (range, 1.2–9 kg). Parameter estimates for the pooled analysis are shown in table 1. Figure 1 demonstrates the quality of fit for pharmacokinetic data over the study time period; each subject's data are connected by a line. Individual concentration predictions are based on values of maximum *a posteriori* Bayesian estimates of the parameters using the *post hoc* option, whereas predicted typical (population) concentrations are based on population parameters and covariate information. The weighted residuals for each subject, with values for each subject joined by vertical bars, are shown in figure 2.

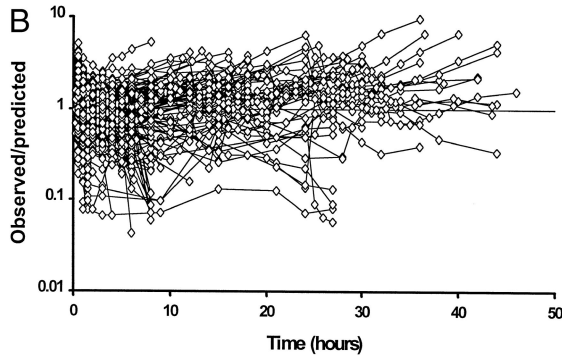
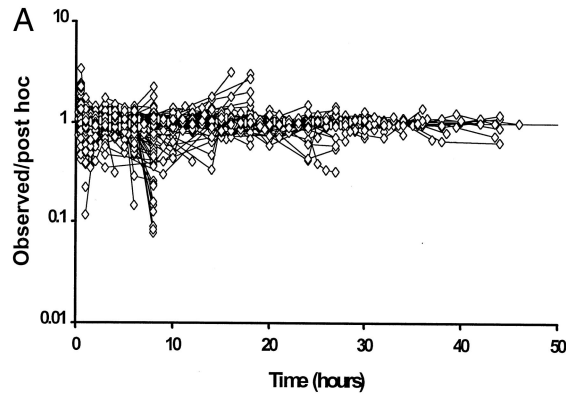


Fig. 1. Quality of fit of pharmacokinetic pooled analysis for all children over the study time. The y-axes display the ratio of measured concentrations to those predicted from pharmacokinetic analysis using a log scale. (A) Values from the NONMEM *post hoc* step based on values of the parameters for the specific individual. (B) Values from the population parameters.

The correlation of between-subject variability for total body clearance and apparent volume of distribution was 0.26, and for between-occasion variability it was 0.14. Variability of Felixir is a major contributor to the latter estimate and would include factors such as minor formulation strength variability, dosing delivery variability, and possible nasogastric loss.

Volume of distribution and clearance changes with age for the pooled analyses are shown in figure 3. Covariate estimates for pooled population parameters are shown in table 2. The volume of distribution decreased exponentially with a maturation half-life of 11.5 weeks from 109.7 l/70 kg at 28 weeks after conception to 72.9 l/70 kg by 60 weeks. Clearance increased from 28 weeks after conception ($0.74 \text{ l} \cdot \text{h}^{-1} \cdot 70 \text{ kg}^{-1}$) with a maturation half-life of 11.3 weeks to reach $10.81 \text{ l} \cdot \text{h}^{-1} \cdot 70 \text{ kg}^{-1}$ by 60 weeks. These values at 60 weeks are 86% of the final values in children. Mean age-related clearance predictions based on the covariate model for clearance are

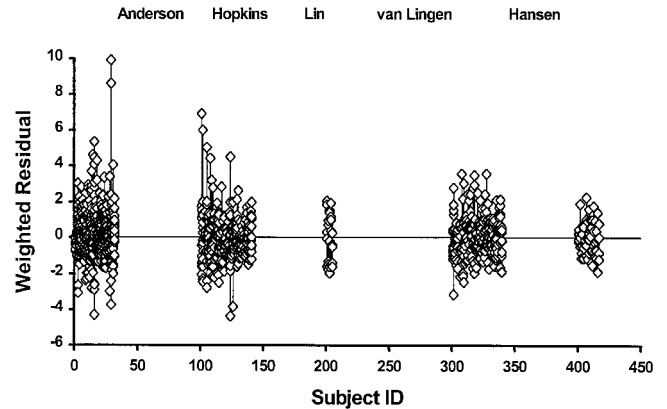


Fig. 2. The weighted residuals for each subject in the subpopulation of infants aged 6 months or less, with values for each subject joined by vertical bars.

shown in table 3. This table also expresses clearance as per kilogram, based on an estimated weight for each postconception age.

The between-occasion variability was 39% for clearance and 8% for the apparent volume of distribution, and clearance between-occasion variability is shown in figure 3B. The between-subject variability for clearance and volume of distribution without covariates in the model were 123 and 78%, respectively; with covariates they were 44% and 20%, respectively (table 1). This difference between between-subject variability without covariates and with covariates is a measure of the predictable decrease in between-subject variability because of covariates. The ω^2 estimates for the different components contributing to variability are shown in table 4. The ratio of the between-subject variability predictable from covariates to the total population parameter variability obtained without covariate analysis gives an indication about how important covariate information is. For example, the ratio of 0.77 achieved for clearance in the current study indicates that 77% of the overall variability in clearance is predictable from covariate information.

The residual errors for the different studies were as follows: studies 1 and 2, 1.31 mg/l; study 3, 0.82 mg/l; study 4, 2.22 mg/l; study 5, 0.90 mg/l; study 6, 1.18 mg/l. Data from Hopkins *et al.*⁶ (study 5) were taken from the published figures, not tabulated results, and consequently had potential for error in addition to the original measurement error. However, the residual error from the data of Hopkins *et al.* was similar to that from the other studies, suggesting that this was a negligible factor.

The absorption half-life for children out of the neonatal period for the oral preparation was 0.21 h (120%) with a lag time of 0.42 h (70%). Oral elixir absorption half-life was delayed in neonates and decreased with a maturation half-life of 0.5 postnatal days (fig. 4). We were unable to show any age-related factors for suppository absorption.

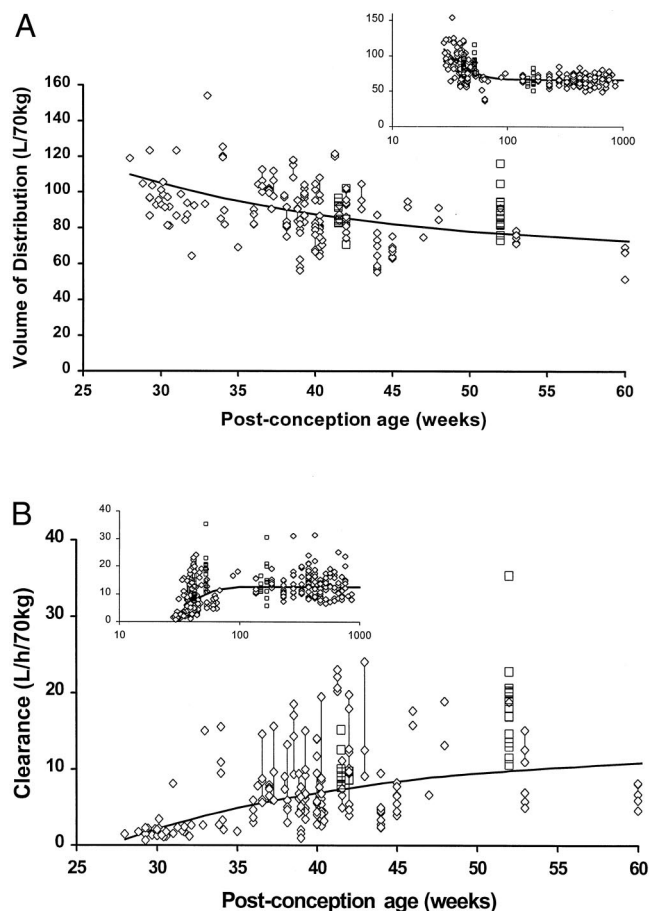


Fig. 3. Clearance and volume changes with age for pooled analysis. The between-occasion variability for each individual is demonstrated by linking estimates with a fine line. Subjects from the study by Hopkins *et al.*⁶ are shown as open squares. (A) Volume of distribution changes with age up to 60 weeks after conception. Individual predicted volumes, standardized to a 70-kg person, from the NONMEM *post hoc* step are plotted against age. The solid line demonstrates the nonlinear relation between volume of distribution and age. The figure inset includes older children and shows the population estimates for apparent volume of distribution of 66.6 l/70 kg reached out of infancy. The x-axis (postconception age in weeks) of the inset figure uses a log scale. (B) Individual predicted clearances, standardized to a 70-kg person, from the NONMEM *post hoc* step are plotted against age up to 60 weeks after conception. The solid line demonstrates the nonlinear relation between clearance and age. The figure inset includes older children and shows the population estimates for clearance of 12.5 l · h⁻¹ · 70 kg⁻¹ reached out of infancy. The x-axis of the inset graph (postconception age in weeks) uses a log scale.

The relative bioavailability of suppository formulations compared with elixir decreased with age (fig. 5). Both the relative bioavailability at 28 weeks and the slope parameter of the triglyceride base were less than the capsule suppository.

Figure 6 shows the predicted concentrations in term neonates given each of the four different formulations. Figure 7 shows simulated mean time-concentration profiles for a term neonate (day 1), a 1-yr-old infant, and a 5-yr-old child given elixir. These simulated profiles were generated from the parameter estimates using the

Table 2. Covariate Models and Estimates for Pooled Population Parameters

Parameter	Estimate
β_{vol}	0.647
Tvol	11.5 weeks
β_{cl}	-0.941
Tcl	11.3 weeks
Tab _s elixir (child)	0.214 h
β_{abs}	49.2
Telix	0.5 day
Slope triglyceride	-0.00513
Slope capsule	-0.00064

β_{vol} and β_{cl} = parameters estimating the fraction above or below V/Foral and CL/Foral, respectively, at 28 weeks' postconception age (PCAGE); Tvol and Tcl = the maturation half-lives of the age-related changes of V/Foral and CL/Foral; β_{abs} = a parameter estimating the fraction above Tab_s at birth; Telix = the maturation half-life of the postnatal age-related change in oral absorption in weeks.

V/Foral = volume of distribution (l/70 kg); CL/Foral = clearance after oral administration (l · h⁻¹ · 70 kg⁻¹).

MKMODEL program.¹⁷ Table 5 shows predicted dosing regimens that achieve a steady trough target concentration of 10 mg/l. The lower relative bioavailability of rectal suppository formulations compared with elixir means that higher doses are required rectally.

Discussion

We describe acetaminophen age-related pharmacokinetic changes from the premature-born neonate through infancy. The estimated age-related pharmacokinetic parameters were then used to predict dose in premature infants using a target concentration approach.⁸

Size was the first covariate used in our analysis of the effects of age and weight. This deliberate choice was based on known biologic principles. A great many physiologic, structural, and time-related variables scale predictably within and between species with weight exponents of 0.75, 1, and 0.25, respectively.⁹ We used these $\frac{1}{4}$ power models in the current study directly as a covariate in the model because these models have well-established principles. The $\frac{3}{4}$ power law for metabolic rates can be derived from a general model that describes how essential materials are transported through space-filled fractal networks of branching tubes.¹⁰ These design principles are independent of detailed dynamics and explicit models and should apply to virtually all organisms.¹¹ By choosing weight as the primary covariate, the secondary effects of age could be investigated. We had no previous biologic model for the effect of age on clearance, apparent volume, or absorption but assumed first-order processes, which are common underlying mechanisms for time-related phenomena.

Clearance increased from 28 weeks after conception (0.741 l · h⁻¹ · 70 kg⁻¹) with a maturation half-life of 11.3 weeks to reach 10.8 l · h⁻¹ · 70 kg⁻¹ by 60 weeks. This

Table 3. Age-related Pharmacokinetic Values Described Using Both the Allometric “ $1/4$ -Power” Model (/70 kg) and Per Kilogram Models (/kg)

Postconception (weeks)	Estimated Weight (kg)	CL _{std} l · h ⁻¹ · 70 kg ⁻¹	CL l · h ⁻¹ · kg ⁻¹	V/Foral _{std} l/70 kg	V/Foral l/kg
28	1	0.7	0.03	102.7	1.47
30	1.3	2.1	0.08	98.8	1.41
34	2.4	4.3	0.14	92.2	1.32
40	3.3	6.8	0.21	84.8	1.21
60	7.5	10.9	0.27	72.5	1.04
1 yr	10	12.3	0.29	67.8	0.97
2 yr	12	12.6	0.28	66.8	0.95
5 yr	20	12.6	0.25	66.8	0.95

CL_{std} = population estimate for CL/Foral; CL/Foral = clearance after oral administration; V/Foral = volume of distribution.

Table 4. Effect of Covariate Analysis on Variance (ω^2)

	PPVt	BSVP	BSVR	BOV	BSVP/PPVt
CL	1.51	1.17	0.19	0.152	0.773
V	0.61	0.56	0.04	0.006	0.925
Telixir	2.13	0.70	1.43	—	0.329
Ftrigly	0.393	0.274	0.119	—	0.697
Fcap	0.589	0.539	0.050	—	0.915

PPVt = the total population parameter variability estimated without covariate analysis; BSVP = the between-subject variability predictable from covariates; BSVR = the random BSV estimated on a parameter when covariate analysis is included; BOV = the between-occasion variability (PPVt = BSVP + BSVR + BOV). The ratio of the between-subject variability predictable from covariates (BSVP) to the total population parameter variability obtained without covariate analysis (PPVt) (*i.e.*, BSVP/PPVt = the fraction of the total variability in the parameter that is predictable from covariates).

CL = clearance; V = volume of distribution; Telixir = absorption half-life of elixir; Ftrigly = relative bioavailability of triglyceride base compared to elixir; Fcap = relative bioavailability of capsule compared to elixir.

estimate is similar to our previous estimate of 3.25 months, based on a smaller neonatal and infant population.⁵ These age-related clearance changes are consistent with immaturity of some of the metabolic pathways responsible for acetaminophen clearance in neonates and infants. Sulfate conjugation is pronounced in neonates and infants, whereas glucuronide conjugation is deficient.^{18,19} The relative contribution of sulfate and glucuronide conjugation changes with age. The usual adult ratio of 2:1 glucuronide to sulfate conjugates of acetaminophen is reached by the age of 12 yr.^{18,19}

The volume of distribution for acetaminophen in mammals,²⁰ including humans, is 0.7–1.0 l/kg, as we would

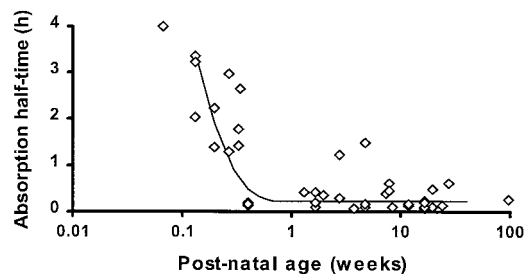


Fig. 4. Oral elixir absorption half-life changes with age. The solid line demonstrates the nonlinear relation between absorption half-life and age.

expect from the allometric size model with a power function of 1. The volume of distribution decreased exponentially with a maturation half-life of 11.5 weeks from 109.7 l/70 kg at 28 weeks after conception to 72.9 l/70 kg by 60 weeks. A lower maturation half-life for the decrease in volume of distribution of 1.9 postnatal days has been previously reported in term neonates,⁵ but that study had few premature infants studied in their first day of life. Fetal body composition and water distribution alters considerably during the third trimester and over the first few months of life.²¹ Acetaminophen has a low molecular weight and reasonable lipid solubility.²² Acetaminophen crosses cell membranes easily and distributes throughout all tissues and fluids²³ but does not bind to plasma proteins. Based on this physiologic argument and the substantially richer data, we now believe that a longer half-life of 11.5 weeks for the decrease in volume is more reasonable.

A large fraction of overall variability in clearance (77%) and volume of distribution (93%) in premature neonates and children is predictable from weight and age. Relatively little variability is accounted for by random between-subject or between-occasion variability (table 4). These findings support the use of weight and age to predict an appropriate dose. Because random between-subject variability is small, there is no indication that measurement of drug concentration and target concentration intervention²⁴ would be of any merit.

The absorption half-life for the oral preparation was 0.21 h (120%) with a lag time of 0.42 h (70%). Oral elixir

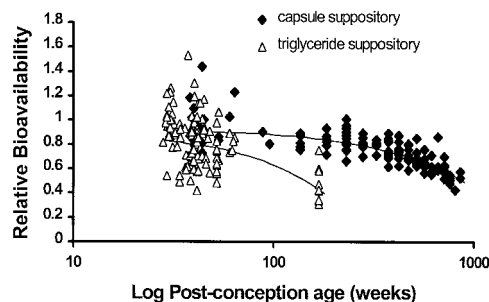


Fig. 5. Changes in relative bioavailability of triglyceride base and capsule suppository formulations with age.

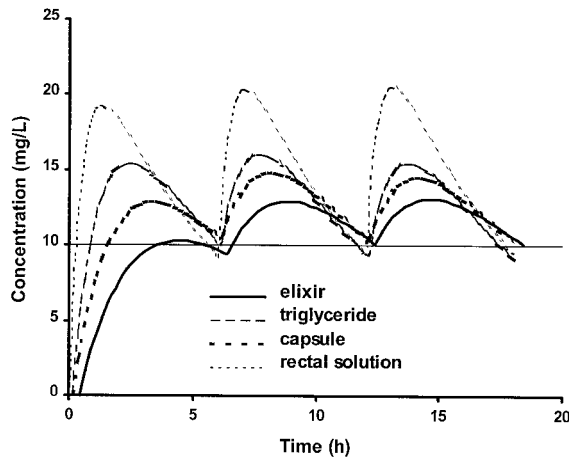


Fig. 6. Simulated mean predicted concentrations at age 40 weeks after conception. Doses in table 3 were used to achieve a trough target concentration of 10 mg/l.

absorption was slow in neonates and decreased rapidly with a maturation half-life of 0.5 postnatal days (fig. 4). Slow absorption in the neonate may be caused by the high levels of maternal gastrin and glucagon transferred to the neonate around birth, but there are a multitude of other factors influencing absorption in the neonate in an intensive care unit, e.g., concomitant medications, body position, enteral feeding, and immaturity of the gastric neuromuscular junction. The ratio of between-subject variability predictable from covariates to total population parameter variability obtained without covariate analysis for the extent of elixir absorption was 0.33, which means that one third of the variability in the extent of absorption is accounted for by maturation processes. The absorption half-life of nasogastric acet-

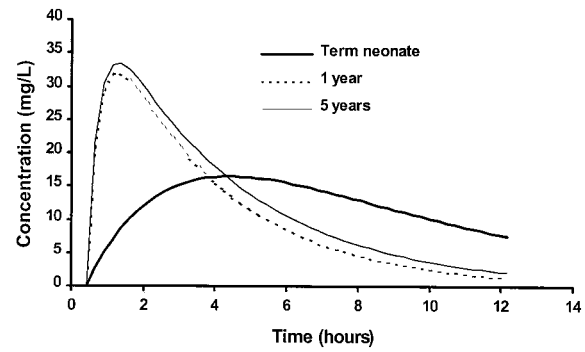


Fig. 7. Simulated mean predicted time-concentration profiles for a term neonate (day 1), a 1-yr-old infant, and a 5-yr-old child given elixir.

aminophen in children given oral elixir has been reported to be as low as 0.04 h.^{25,26} The absorption half-life reported in adult series after oral administration ranges from 0.06 to 0.6 h.²⁰ Acetaminophen absorption depends on gastric emptying, which is slow and erratic in the neonate.²⁷ Normal adult rates may not be reached until 6–8 months.^{28–31} However, we were unable to demonstrate this trend in our current analysis. The rectal solution was the most rapidly absorbed rectal formulation (absorption half-life, 0.33 h) in the premature neonate, which we assumed was because of an absence of the dissolution phase required by suppositories. Absorption parameters for the triglyceride base (absorption half-life, 0.80 h; coefficient of variation, 101%) and capsule suppositories (absorption half-life, 1.38 h; clearance variability, 57%) were similar to those described in older children and adults.^{20,26,32} There was no detectable lag time for absorption with the rectal solution formulation.

Table 5. Dosing Regimens that Attain an Approximate Mean Steady State Target Through Concentration of 10 mg/l

	Loading Dose (mg/kg)	Maintenance Dose (mg/kg)	Dosing Interval (h)	Daily Maintenance Dose (mg · kg ⁻¹ · day ⁻¹)
Oral dosing regimens				
30 weeks	25	12	12	24
34 weeks	25	15	8	45
40 weeks	25	15	6	60
60 weeks	25	15	4	90
Rectal dosing regimens				
Triglyceride suppository				
30 weeks	35	15	12	30
34 weeks	35	20	8	60
40 weeks	35	20	6	80
60 weeks	35	20	4	120
Capsule suppository				
30 weeks	30	12.5	12	25
34 weeks	30	17.5	8	52.5
40 weeks	30	17.5	6	70
60 weeks	25	15	4	90
Solution				
30 weeks	40	20	12	40
34 weeks	45	25	8	75
40 weeks	45	30	6	120
60 weeks	45	25	4	150

This suggests that gastric emptying may be the primary determinant of a lag time for absorption after oral administration.

The relative bioavailability of the triglyceride base and capsular suppository relative to elixir decreased with increasing age. This role of maturation processes appears to be even more important (ratio of between-subject variability predictable from covariates to total population parameter variability obtained without covariate analysis: 0.697 and 0.915, respectively) for the extent of rectal absorption of these formulations than that seen with oral absorption of the elixir. This relation between age and relative bioavailability may be attributable to rectal insertion height and consequent rectal venous drainage patterns.³³ The rectal route has the potential to partially reduce first-pass hepatic loss by draining into the inferior and middle hemorrhoidal veins. Acetaminophen has a hepatic extraction ratio of 0.11–0.37 in adults.³⁴ Bioavailability consequently depends on site of absorption within the rectum.^{35,36} Coulthard *et al.*³⁷ reported a relative bioavailability of 0.78 (95% confidence interval, 55, 101) for triglyceride base and capsule suppositories in children. A lower relative bioavailability in older children of 0.54²⁶ for the capsule suppository and 0.3³⁸ for the triglyceride base is consistent with these age-related changes. The slope parameter describing the relative bioavailability of the triglyceride base is heavily influenced by only nine children from the data of Hopkins *et al.*⁶ Consequently, we have less confidence in our relative bioavailability prediction for this formulation out of the neonatal period. We are unable to explain the reduced relative bioavailability of the rectal solution compared with the suppository formulation, but this may be attributable to loss from the rectum. Because this loss per rectum may not be consistent in all children, caution should be applied before giving substantially larger rectal doses.

A target concentration of 10 mg/l is the steady state concentration that is reported to reduce temperature to 50% of the maximum possible temperature reduction in febrile children³⁹ and is also the effect-site concentration associated with pain scores less than 6 (of a possible 10) in 90% of children after tonsillectomy.²⁶ Painful stimuli in neonates may not be equivalent to tonsillectomy pain in older children, and a target concentration for such pain in neonates has not been defined.⁴ However, the target concentration approach allows us to compare dose regimens at different ages and to predict dose for alternative target concentrations because dose is linearly related to concentration. The dosing schedules proposed in table 3 result in a steady state concentration of approximately 10 mg/l at trough. However, neonates with reduced clearance will achieve higher concentrations. Neonates are also capable of forming hepatotoxic metabolites, despite a relatively low level of activity of the cytochrome P-450 CYP2E1 enzyme system.^{40,41} It is

currently impossible to predict which individuals have an enhanced susceptibility to cellular injury from acetaminophen. The coingestion of therapeutic drugs, food, or other xenobiotics has potential to induce this isoenzyme.⁴² The influence of disease on acetaminophen toxicity is unknown. Consequently, even the proposed regimens may cause hepatotoxicity in some individuals if used for longer than 2–3 days.⁴²

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