Pharmacokinetics of Sirolimus-Eluting Stents Implanted in the Neonatal Arterial Duct

Kyong-Jin Lee, MD; Winnie Seto, PharmD, MSc; Lee Benson, MD; Rajiv R. Chaturvedi, MRCP(UK), MD, PhD

Background—Sirolimus-eluting stents may have clinical advantages over bare-metal stents in the extremely proliferative environment of the neonatal arterial duct. However, sirolimus has immunosuppressive actions and little is known regarding sirolimus pharmacokinetics in the newborn.

Methods and Results—This is a retrospective review of sirolimus pharmacokinetics in neonates who underwent sirolimus-eluting stent implantation in the arterial duct for pulmonary blood flow augmentation. Pharmacokinetic parameters were obtained by noncompartmental analysis and by a Bayesian one-compartment nonlinear mixed model. Nine neonates received a single sirolimus-eluting stent with a total sirolimus dose of 245 μg (n=1), 194 μg (n=5), or 143 μg (n=3). Peak sirolimus concentrations were 13.6±4.5 μg/L (24.8 μg/L highest) and clearance was 0.042±0.03 L/hour (noncompartmental analysis) and 0.051 L/hour (95% credible intervals 0.037–0.069, nonlinear mixed model). Sirolimus remained >5 μg/L, the trough level used in oral immunosuppressive therapy, for (95% credible interval) 15.9 (11.4, 22.8), 12.9 (7.6, 19.0), and 8.4 (2.3, 14.5) days for the 245, 194, and 143 μg sirolimus dose stents, respectively. Estimates of the duration of systemic immunosuppression are provided for combinations of 2 stents.

Conclusions—In neonates after sirolimus-eluting stent implantation, peak sirolimus levels were 20× higher and clearance 30× lower than previously reported in older children and adults. Sirolimus levels were within the immunosuppressive range for a prolonged period, but with no observable clinically significant adverse outcomes.

Key Words: congenital heart disease ▪ drug-eluting stent ▪ ductus arteriosus ▪ neonate ▪ pharmacokinetics ▪ sirolimus

Stent implantation is a recognized management option in maintaining arterial duct patency in newborns with duct-dependent pulmonary blood flow, but with bare metal stents the reintervention rate (redilatation or need for a surgical shunt) is 17% to 25% at 6 months.1–3 The neointimal proliferative process associated both with spontaneous ductal closure and in reaction to stent implantation compromises luminal diameter.4–7 In this regard, sirolimus, an immunosuppressive agent with anti-inflammatory and antiproliferative effects, has theoretical benefits.8,9 Drug-eluting stent technology enables topical drug delivery with therapeutic drug concentrations locally within the blood vessel wall, despite substantially lower systemic blood levels.10 Sirolimus-eluting stents (SES) are effective and safe in adult coronary arteries.11 SES implanted in the porcine neonatal arterial duct have higher patency rates compared with bare-metal stents and also exhibit an antiproliferative action on arterial duct smooth muscle.12 Pharmacokinetic studies of SES in adult pigs10 and humans13 have shown low peak serum drug levels occurring at 1 and between 3 and 4 hours, respectively, with minimal detectable levels by 3 and 7 days, respectively. SES implantation has been reported in children, but little is known regarding subsequent pharmacokinetics in the pediatric population.14–19 The youngest patient previously reported was 3 months old at the time of SES implantation in the right ventricular outflow tract (peak 8 μg/L, undetectable between 12 and 37 days15), and to our knowledge, there are no reports of neonatal use. Sirolimus experience in the pediatric population is predominantly in the form of oral immunosuppressive therapy in transplant recipients. Dosage is titrated by steady-state trough levels (target 5–15 μg/L).20,21

In this study, we report the pharmacokinetics of sirolimus after single SES implantation in the neonatal arterial duct. Model-free point estimates were obtained by noncompartmental analysis, and in addition, a one-compartment Bayesian population pharmacokinetic model was used to provide point estimates with credible intervals, and this also allowed the prediction of pharmacokinetics if 2 stents had been implanted.
WHAT IS KNOWN

- Bare metal stents implanted in the human neonatal arterial duct are associated with a 17% to 25% re-intervention rate at 6 months.
- Sirolimus-eluting stents implanted in the porcine neonatal arterial duct have higher patency rates than bare metal stents.
- Sirolimus-eluting stents in adults result in low systemic sirolimus levels.

WHAT THE STUDY ADDS

- Implantation of sirolimus-eluting stents in human neonatal arterial ducts resulted in high peak systemic sirolimus levels and slow clearance.
- Although systemic sirolimus levels remained in the immunosuppressive range for a prolonged period of time, there did not seem to be any adverse clinical sequelae attributable to immunosuppression.

Methods

Sirolimus-eluting Cypher Select (Cordis Inc., Miami, FL) stents were fully approved for human use by Health Canada during this period. Pediatric systemic sirolimus levels after SES had not been reported at the start of this clinical series and were expected to be low based on the adult literature and estimates by a Pediatric Clinical Pharmacologist (12). We thought it prudent to measure sirolimus levels prospectively for the purposes of clinical monitoring/quality assurance because symptoms consistent with infection or necrotizing enterocolitis occur frequently in these neonates. This enabled physicians involved in their direct care to interpret clinical events in the context of whether there was systemic immunosuppression. Each candidate for ductal stenting was discussed at a joint Cardiology and Cardiovascular Surgery case conference before referral for catheterization. Parents provided consent for use of a SES and for a clinical protocol of serial sirolimus measurements that were coordinated with blood samples taken for other clinical reasons.

The hospital Research Ethics Board approved the pharmacokinetic analysis and dissemination of this clinical data. All stents were 3.5 mm diameter, and the sirolimus dose was dependent on the stent length. A drug-free polymer layer has been applied on top of the drug-polymer matrix as a diffusion barrier to prolong the release of the drug with 50% of the sirolimus eluted over the first week, 80% over 30 days, and 100% over 90 days. Sirolimus levels were coordinated with blood sampling for other clinical reasons and drawn at 1, 3, 24 hours poststent insertion followed by every 7 days until the sirolimus level was below the limit of quantification (<1 μg/mL) where feasible. Sirolimus levels from whole blood samples (40 μL) of patients were analyzed by a LC-MS/MS (liquid chromatography tandem mass spectrometer)—4000 QTrap at the Therapeutic Drug Monitoring Laboratory, Hospital for Sick Children. The assay has a precision (defined by percentage of coefficient of variation) of 6.8% for quality control level of 6 μg/L, 6.8% for quality control level of 12.8 μg/L, and 7.4% for quality control level of 23 μg/L, respectively.

Secondary data collection included cardiac diagnoses, review of the procedural aspects of the patent ductus arteriosus (PDA) stent implantation and any other subsequent catheter or surgically based cardiac interventions, and clinical outcomes, including ductal stent patency, which was determined by echocardiography.

Data Analysis

Two techniques were used for pharmacokinetic modeling of sirolimus levels: (1) point estimates by noncompartmental analysis of each subject using trapezoidal integration (R-3.1.1,22 package PK.1.3–2) and (2) a single intravenous dose one-compartment nonlinear mixed effects model (NLMM23 to obtain population estimates with 95% credible intervals (model in the Data Supplement). Wakefield’s WinBUGS script24 was adapted to run with JAGS 3.4.0,25 and because the concentration-time data were a ragged array (a different number of data points for each subject), nested indexing was used to specify the subject to which each observation belonged (Data Supplement).26 The JAGS output was analyzed with coda-0.16–1.27 Rate constants are positive, and hence, lognormal priors are often used in pharmacokinetic studies. Model fitting with log normal priors was sensitive to initial values, and chain adaptation/equilibration often failed. This was particularly the case for the sparse data points in the rising phase of sirolimus concentrations and kₚ, the associated rate constant for the rising phase. Gaussian priors were used instead, with convergence of 3 different chains demonstrated by traceplots, and resulted in unimodal densities for each parameter and fitted data point. Credible intervals for population pharmacokinetics were obtained from 10⁴ simulations of the one-compartment model, using the population parameters from the NLMM for each of the sirolimus doses (245, 194, and 143 μg).

The time for sirolimus concentration to fall to 5 μg/L was estimated by linear interpolation for both the raw data and the one-compartment model. Bioavailability of 100% was assumed throughout.

Results

Nine newborns underwent single SES implantation in the arterial duct. The specifications of the implanted Cypher Select stents were 3.5×13 mm (143 μg) in 3 patients, 3.5×18 mm (194 μg) in 5 patients, and 3.5×23 mm (245 μg) in 1 patient.

Patient Characteristics

The median age at implantation was 10 days (range 1–17). The median weight at time of implantation was 3.2 kg (range 2.4–4.3). Cardiac diagnoses, cardiac procedures, and arterial duct stent follow-up for each patient are summarized in Table 1. All patients are alive at a median follow-up of 3.2 years (range 172 days to 5.3 years).

Noncardiac comorbidities included one infant born at gestational age 35 weeks after having undergone in-utero laser ablation for twin to twin transfusion, who developed necrotizing enterocolitis and pneumoperitoneum with ischemic bowel perforation requiring surgical anastomosis at 11 days (6 days before arterial duct stent implantation). One patient had dysmorphism, vertebral anomalies, and bilateral renal pelviectasis. One patient had microdeletion 22q11 and a solitary kidney.

PDA Anatomy

All PDA stents were implanted for the purpose of providing pulmonary blood flow. The stents were implanted into the 3 types of PDA anatomy: left aortic arch with PDA from descending aorta (n=5), right aortic arch with PDA from left innominate artery (n=3), and right aortic arch with PDA from aorta (n=1; Figure 1).

Stent Implantation Procedure

All infants were anaesthetized, intubated, and mechanically ventilated during the PDA stent implantation cardiac catheterization. Vascular access was obtained at the discretion of the operator for optimal stent implantation (femoral artery [n=4], femoral vein [n=1], femoral artery and vein [n=3], and carotid artery [n=1]). Angiography delineated arterial duct anatomy.
A 0.014" Wizdom wire (Cordis Corporation, Miami, FL) was placed across the arterial duct either from the pulmonary artery or aorta. Additional stiffer 0.014" wires were used as needed. The stents were placed such that the implants protruded into the main pulmonary artery, but were flush with the aorta. One Cypher Select was implanted into each patient. Additional bare-metal stents were implanted as deemed necessary. Four additional bare-metal stents were implanted in 3 patients. In one patient, the Cypher Select stent migrated forward during removal of the balloon catheter. The stent was manipulated partially back into the PDA and 2 bare-metal stents were subsequently implanted to cover the entire arterial duct, leaving the SES in situ. One patient required an additional bare-metal stent (3.5×15 mm) to allow for full coverage of the PDA. One patient had bilateral PDA, and the right PDA was stented with a 3.5×15 mm bare-metal stent.

Two of the SES were not implanted in the desired position. As previously mentioned, in one patient, the DES migrated during balloon catheter removal, necessitating additional bare-metal stent implantations. In the second patient, the SES embolized into the right pulmonary artery during guidewire removal. This stent was surgically removed 12 days later. Sirolimus levels were monitored before surgery.

Three patients required additional procedures on the PDA stented with an SES (Table 1). An additional bare-metal stent was implanted within the sirolimus-eluting stented PDA in one patient for significant neointimal proliferation, and the sirolimus-eluting stent was redilated in 2 patients.

### Anticoagulation/Antiplatelet Regimen

After stent implantation, patients were maintained on ≥1 anti-coagulation or antiplatelet drug therapies, which consisted of low molecular weight heparin (n=7), clopidogrel (n=5), and acetylsalicylic acid (n=4). Drug therapy was maintained until the patency of the stented PDA was no longer deemed to be necessary for clinical well-being or until complete closure of the stented PDA was documented.

### Clinical Outcomes

Seven patients underwent 2 ventricle repair, of which 2 have residual atrial septal defects and 2 patients underwent a Fontan procedure with one developing plastic bronchitis (Table 1).

### PDA Stent Outcomes

The sirolimus-eluting PDA stent embolized at the time of implantation in 1 patient with surgical removal 12 days later.
(Table 1). Excluding this patient, the median time of documented stent patency or time to surgery which obviated further need for ductal patency was 160 days (range 39–813 days). For the 2 single ventricle patients, the PDA stent remained patent until the time of the bidirectional cavopulmonary connection at 126 and 149 days of age. In the 3 patients who underwent biventricular repair, the stented PDA was patent up to the time of complete repair. In those 3 patients who did not require surgery, the stented PDA was documented to be completely occluded at 359, 426, and 1198 days.

Three patients exhibited signs of infection. One patient who had previously undergone surgery for necrotizing enterocolitis developed fever 9 days after PDA stent implantation with an elevated white blood cell count (28.0×10⁹/L) and a positive blood culture for coagulase negative staphylococcus and was treated with antibiotics for a central venous line infection. One patient exhibited an elevated white blood cell count (29.4×10⁹/L) 1 day after stent implantation and was treated empirically with broad spectrum antibiotics for 5 days. Blood cultures were negative. One patient developed fever 34 days after stent implantation and was treated for a positive urine culture for *Escherichia coli*. No patient developed leukopenia (<5×10⁹/L), while sirolimus levels were detectable.

Two patients exhibited signs of necrotizing enterocolitis. One patient had occult blood positive stools and a negative ultrasound, but was treated with total parenteral nutrition and antibiotics. One patient experienced necrotizing enterocolitis before ductal stent implantation with no recurrence.

Liver function tests were performed in 8 patients, with 1 patient demonstrating abnormalities, which coincided with a metabolic acidosis and increased lactate consistent with decreased cardiac output. In this patient, aspartate aminotransferase and alanine aminotransferase remained mildly elevated 5 months after stent implantation in the setting of sirolimus levels being nondetectable at 2 months.

![Figure 1. Angiograms of arterial duct stenting are shown. A, Lateral projection of arterial duct (*) originating from left descending aorta. B, Stented arterial duct of A. C, Frontal projection of arterial duct (*) originating from the left innominate artery of a right aortic arch. D, Stented arterial duct of C.](image1)

![Figure 2. Concentration–time curves for sirolimus in 9 neonates. The target minimal trough level, for patients receiving oral sirolimus for immunosuppression, is 5 μg/L (horizontal red line). Note the sparsity of data in the rising phase of the curve and the second peak in concentration seen in some patients (1, 3, 5, 7).](image2)
Sirolimus Pharmacokinetics

Concentration–time curves showed fast sirolimus release from the stent, high peak concentrations, and a subsequent slow fall (Figure 2). The rising phase of sirolimus levels was captured in 4 subjects (3, 4, 5, 8) with at least one measurement before the peak (patient 3 had 2), but for the other 5, the first measurement was the highest. The small number of data points available for modeling the rising phase resulted in wide credible intervals for the rate constant of the rising phase ($k_a$). A biphasic release of sirolimus in the first 12 hours was seen in 4 subjects (1, 3, 5, 7; Figure 2), and these data were smoothed rather than modeled (Figures 2 and 3). The duration of time that the sirolimus concentration was $>5 \mu g/L$ was found by linear interpolation (Table 2) for both the measured concentrations and the predictions of the population model. In 3 patients (3, 6, 8), there was a wide time interval between samples during which the concentration fell $<5 \mu g/L$, and hence linear interpolation of the raw data will overestimate the time interval that the sirolimus concentration was in the immunosuppressive range. The estimates from the one-compartment model are likely more accurate in these cases.

Noncompartmental analysis and the Bayesian one-compartment NLMM showed good agreement for all measured parameters, with the point estimates by noncompartmental analysis falling within the NLMM 95% credible intervals (Table 2). The majority of the measured concentration–time data lies within the 95% credible intervals for the population one-compartment model (Figure 3; individual fits in the Data Supplement).

Complete coverage of many arterial ducts requires >1 stent. Using the population parameters from the NLMM, predictions were made of the pharmacokinetics for different combinations of 2 stents (Table 3), that is, higher sirolimus doses. The highest sirolimus dose (490 $\mu g$) with 2x23 mm stents had a peak level of 31.9 $\mu g/L$ (95% credible intervals, 20.9, 49.5) and remained within the immunosuppressive range for 22.8 days (95% credible intervals, 19.0, 28.5).

Additional Data on 2 Older Patients to Contrast With Neonatal Pharmacokinetics

SES were implanted into 2 older patients. One patient was 2.2 years old, weight 12.5 kg, with a stent 2.5x12 mm (124 $\mu g$ sirolimus) implanted into the left main coronary artery whilst on extracorporeal membrane oxygenation support. During the 7 days of extracorporeal membrane oxygenation, 8 sirolimus levels were obtained: peak 2.7 $\mu g/L$ (3 hours), 1.3 $\mu g/L$ (3 days), 1.2 $\mu g/L$ (9 days) and nondetectable at 21 days. In another patient, 4 years old, weight 17.1 kg, a stent (3.5x18 mm, 194 $\mu g$ sirolimus) was implanted into a left pulmonary vein. Drug levels were 3.7 and 3.1 $\mu g/L$ at 1 and 3 hours, respectively, after implantation. The stent remains patent 2.7 years post-implantation with a mean gradient 3 mmHg.

Discussion

This is the first report of drug-eluting stent implantation in the arterial duct of human neonates, a blood vessel in which a robust neointimal proliferative process is an essential part of the normal developmental program that results in closure within a few days after birth.3–7 Higher stent patency and
decreased neointimal proliferation were found with SES in comparison to bare-metal stents when implanted in the neonatal porcine duct. Our objective was to establish the pharmacokinetics of SES in human neonates because sirolimus is also an immunosuppressive agent, before more extensive neonatal use. In this pilot study, we only used a single SES even if multiple stents were required to cover the whole arterial duct. A comparison of the clinical efficacy of drug-eluting with bare-metal stents in the neonatal arterial duct is beyond the scope of this study (small number of patients and both SES and bare-metal stents in the same duct), but the SES maintained their potency to the desired clinical duration.

To our knowledge this is the largest series of neonatal patients with sirolimus pharmacokinetics, with unique observations: peak sirolimus levels were 20 to 40 times higher and clearance with sirolimus pharmacokinetics, with unique observations:

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<th>Cmax, μg/L</th>
<th>Time to Cmax, h</th>
<th>Time &gt;5 Cmax, μg/L, days</th>
<th>Cl ×10⁻², L/h</th>
<th>Half-Life, h</th>
<th>AUC ×10², μg h/L</th>
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<th>Population estimate</th>
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<td>16.2 (13.0, 21.0)</td>
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<td>21.9</td>
<td>18.2 (14.9, 23.2)</td>
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<td>19.9 (16.5, 25.2)</td>
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<td>4</td>
<td>28.5</td>
<td>21.4 (17.8, 26.9)</td>
</tr>
<tr>
<td>5</td>
<td>31.9</td>
<td>22.8 (19.0, 28.5)</td>
</tr>
</tbody>
</table>

Data for the one-compartment nonlinear mixed model are presented as 50th (2.5th, 97.5th) quantiles. AUC indicates area under the concentration–time curve; £max indicates peak concentration. £max, clearance; £e, rate constant for drug elution from stent; and £k, rate constant for elimination.

Hence, the low clearance of sirolimus eluted from stents in neonates compared with older children and adults is likely related to age-dependent maturation of cytochrome P450 enzymes. This liver enzyme immaturity has implications for neonatal use of all current drug-eluting stents, both of the rapamycin-family (everolimus, zotarolimus, and umirolimus) and those based on paclitaxel because both compounds are predominantly metabolized by cytochrome P450 and cleared by the liver. High peak levels and slow clearance should be anticipated with these drugs as well.

Pharmacokinetic parameters were not discernibly affected by simultaneous use of enoxaparin, aspirin, or clopidogrel. Cytochrome P450 enzymes are not involved in asparagus metabolism.31 Clopidogrel is activated by CYP2C19, and
some reports suggest that CYP3A4, which participates in sirolimus metabolism, may also be involved.\textsuperscript{12,13} Pharmacokinetic studies of SES in adult humans have shown low peak serum drug levels occurring between 3 and 4 hours (1 stent, 0.57±0.12 μg/L; 2 stents, 1.05±0.39 μg/L) with minimal detectable levels by 7 days and clearance of 1.46±0.45 L/hour.\textsuperscript{14} The experience of drug-eluting stents in children is limited,\textsuperscript{14,15,17–19,33} with only 2 reports of drug level monitoring. In a 5.3 kg, 3-month-old infant with a 143 μg sirolimus stent implanted into an obstructed right ventricular outflow tract conduit, 5 drug levels were measured over 35 days.\textsuperscript{15} Serum levels peaked between 7 and 8 μg/L within the first 2 days, were below 3 μg/L after 7 days, and undetectable at 5 weeks. An 8-month-old, 4.6 kg infant underwent paclitaxel) of a previously implanted bare-metal stent in 2 stents of 113 μg of everolimus-eluting stent (113 μg) implantation and a paclitaxel-coated balloon dilation (coated with 640 μg of paclitaxel) of a previously implanted bare-metal stent in 2 stents of 3–6 μg/L) at 24 hours. Our experience with the 2 older patients demonstrated similar pharmacokinetic profiles to the published reports.

Infection, necrotizing enterocolitis, and abnormal liver function tests are not uncommon clinical problems in newborns with duct-dependent pulmonary blood flow, and it is difficult to attribute the episodes experienced by our patients as being secondary to systemic sirolimus. This is illustrated in the one patient who had necrotizing enterocolitis before stent implantation. The one patient with abnormal liver function tests had persistently mildly elevated transaminases even when sirolimus levels were not detectable. There were no long-term clinical consequences from any of these complications. Consideration should be given to delaying live vaccine administration, while sirolimus levels remain in the immunsuppressive range, especially if 2 SES are used (Table 3).

Limitations
The main limitations of this report are the small number of patients and the incomplete concentration–time drug level profiles for several patients, in particular the sparse data in the rapid early elution phase in the first 120 minutes after stent implantation. Hence, our estimates of rising-phase kinetics are based on a small number of data points, and we are likely to have missed the true sirolimus peak levels and underestimated the rate constant for elution. However, estimates of elimination phase kinetics are robust, in particular clearance and duration of systemic immunosuppressive sirolimus levels. Despite these limitations, this is the most detailed pharmacokinetic description of SES in the neonatal population. Given the developmental increase in the cytochrome P450 family enzyme activity during infancy, our numeric values do not extrapolate to older children.

Conclusions
Pharmacokinetics are important for any clinical drug delivery system. In this first neonatal SES report, sirolimus levels were higher and clearance lower by an order of magnitude as compared with adults. However, prolonged immunosuppressive levels of sirolimus were well tolerated. Similar high systemic drug levels should be anticipated in neonates with all the other currently available drug-eluting stents.

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We acknowledge the contribution of Warren Walsh, Resource Technologist, Therapeutic Drug Monitoring laboratory, Hospital for Sick Children who assisted in the analysis of the sirolimus samples.

Disclosures
None.

References


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Supplemental Material

Pharmacokinetics of sirolimus-eluting stents implanted in the neonatal arterial duct.
Supplemental Methods

The single i.v dose 1-compartment model, parameterized by clearance (equation 9.30 from page 478 of [1]) is:

\[ Y = D \left( \frac{ka \cdot ke}{Cl \cdot (ka - ke)} \right) \left( \exp[-ke \cdot t] - \exp[-ka \cdot t] \right) \]

\( Y \), sirolimus concentration (\( \mu g/L \))

\( D \), sirolimus dose (\( \mu g \))

\( Cl \), clearance (\( L/hr \)). \( Cl = V \cdot ke \), where \( V \) is the volume of distribution (\( L \)).

\( ka \), rate constant for rising phase i.e elution from the stent (hr\(^{-1}\))

\( ke \), rate constant for elimination phase (hr\(^{-1}\))

\( t \), time (hr)
Minor changes were made to Wakefield’s WinBUGS script [2] for JAGS 3.4.0 with nested indexing [3] to specify which child each observation belonged to. This is the model file:

```r
var Y[Nobs], time[Nobs], child[Nobs], mu[Nobs], fitted[Nobs], resid[Nobs], theta[N, 3]

model
{
  # loop across all Nobs observations (Y[i] at time[i], with each Y[i] belonging
  # to a child[i]).
  for(i in 1:Nobs){
    Y[i] ~ dnorm(mu[i], eps.tau)
    mu[i] <- dose.ug[child[i]] * 
      exp(theta[child[i], 1] + theta[child[i], 2] - theta[child[i], 3]) * 
      exp(-exp(theta[child[i], 1])*time[i]) - 
      exp(-exp(theta[child[i], 2])*time[i]) / 
      (exp(theta[child[i], 2])-exp(theta[child[i], 1]))
    fitted[i] <- mu[i]
    resid[i] <- Y[i] - fitted[i]
  }
  # loop across N children for child specific values of parameters
  # ke, ka, Cl
  for(j in 1:N){
    theta[j, 1:3] ~ dmnorm(beta[1:3], Dinv[1:3, 1:3])
    ke[j] <- exp(theta[j, 1])
    ka[j] <- exp(theta[j, 2])
    Cl[j] <- exp(theta[j, 3])
  }
  logtau ~ dunif(0.001, 1000)
  eps.tau <- exp(logtau)
  sigma <- 1 / sqrt(eps.tau)
  Dinv[1:3, 1:3] ~ dwish(R[1:3, 1:3], 3)
  beta[1:3] ~ dmnorm(mean[1:3], prec[1:3, 1:3])
  # population values for ke, ka and Cl are kemed, kamed, Clmed respectively
  kemed <- exp(beta[1])
  kamed <- exp(beta[2])
  Clmed <- exp(beta[3])
}
```
Individual fits
child 5

Concentration (µg/L) vs Time (days)
child 6

Concentration (µg/L) vs. Time (days)
child 7

Concentration (µg/L)

Time (days)
child 9

Concentration (µg/L) vs Time (days)
Supplemental References

2) http://faculty.washington.edu/jonno/book/THeophWinBUGS.txt