

Randomized Population Pharmacokinetic Analysis and Safety of Intravenous Acetaminophen for Acute Postoperative Pain in Neonates and Infants

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Abstract

Intravenous administration of acetaminophen is an alternative to the oral and rectal routes, which may be contraindicated in particular clinical settings. This randomized, placebo-controlled study of intravenous acetaminophen (Ofirmev, Mallinckrodt Pharmaceuticals, Bedminster, New Jersey) in neonate and infant patients with acute postoperative pain assessed pharmacokinetics (PK) and safety, in addition to efficacy and pharmacodynamics of repeated doses administered over 24 hours. Neonate and infant patients (<2 years of age) who were undergoing surgery or had experienced a traumatic injury and were expected to need pain management for at least 24 hours were enrolled. Subjects were randomly assigned to receive intravenous acetaminophen low dose, intravenous acetaminophen high dose, or placebo. A population PK model of intravenous acetaminophen was updated by combining 581 samples from the current study of 158 neonate and infant subjects with results from a previously developed model. The individual predicted-versus-observed concentrations plots showed that the structural PK model fit the blood and plasma acetaminophen concentration-versus-time profiles in the active and placebo groups. Terminal elimination half-life was prolonged in neonates and younger infants and in intermediate and older infants similar to values in adults. When compared with placebo, total rescue opioid consumption was similar and significantly fewer intravenous acetaminophen patients prematurely discontinued because of treatment-emergent adverse events ($P < .01$). For intravenous acetaminophen, neonates receiving 12.5 mg/kg every 6 hours had PK profiles similar to younger, intermediate, and older infants, adolescents, and adults weighing <50 kg receiving 15 mg/kg every 6 hours and adults ≥ 50 kg receiving 1000 mg every 6 hours.

Keywords

acetaminophen, acute postoperative pain, infants, neonates, opioids

Acetaminophen (known outside the United States by its International Nonproprietary Name, paracetamol) is an analgesic and antipyretic agent used widely in both adult and pediatric populations. Administration of acetaminophen via the oral and rectal routes may be problematic; the former may be contraindicated for patients who are nothing by mouth, and the latter is associated with unpredictable plasma concentrations. In the United States, intravenous acetaminophen (Ofirmev, Mallinckrodt Hospital Products, Inc., Hazelwood, Missouri) is approved for the management of mild to moderate pain in pediatric patients 2 years of age and older (and adults, including those >65 years of age) and for the reduction of fever in pediatric patients and adults.

Prior pharmacokinetic (PK) studies have demonstrated that exposure levels of intravenous acetaminophen in children and adolescents are similar to adults but higher in neonates and infants.^{1,2} The study by Zuppa and colleagues included 3 neonates, 25 infants, 25 children, and 22 adolescents, and the study

by Palmer and colleagues included 43 neonates and 7 infants. Data from these 2 PK trials were combined

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for a population PK meta-analysis, PK modeling, and several dose simulations. This merged data set resulted in 125 neonate and infant subjects with 1260 acetaminophen concentration values for inclusion in the analysis. The developed model was a 2-compartment structural model with linear elimination and size effect on PK parameters, which fitted the concentration-time profiles of acetaminophen adequately in the pediatric population from the studies by Zuppa and Palmer.

Previous models demonstrated that PK parameters in neonates and infants were comparable to adolescent and adult populations after compensating for both significantly decreased clearance and longer terminal elimination half-life ($t_{1/2}$). Dosing simulations from PK data in infants and neonates suggested that dose reductions of 33% in infants 1 month to <2 years of age and 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce a PK exposure similar to that observed in children ≥ 2 years of age.

The current study sought to update the prior population PK model of intravenous acetaminophen in neonates and infants; in addition, efficacy, pharmacodynamics (PD), and safety were assessed.

Methods

Prior to initiation of this randomized, placebo-controlled multicenter study of intravenous acetaminophen for the treatment of acute pain, the protocol was reviewed and approved by each site's institutional review board. A list of the names and locations of all the participating study sites can be found in the online appendix. Neonate and infant patients <2 years of age were eligible to participate if they were scheduled to undergo surgery or had experienced a traumatic injury and were expected to need pain management for at least 24 hours. Each eligible subject's parent or guardian provided written informed consent prior to the subject's participation in the study. Subjects were divided into 4 age groups: neonates (<28 days), younger infants (28 days to <6 months), intermediate-age infants (6 months to <12 months), and older infants (12 months to <24 months). Neonates were further categorized into extreme preterm neonates (≥ 28 to <32 weeks' gestational age), preterm neonates (≥ 32 to <37 weeks' gestational age), and full-term neonates (≥ 37 weeks to ≤ 40 weeks' gestational age).

During a 6-hour preassessment period, all eligible subjects received a protocol-specified opioid at a bolus dose according to the investigator's clinical discretion and the center's analgesic protocol, if applicable, and then were randomly assigned to 1 of 2 intravenous acetaminophen plus standard-of-care (SOC) opioid dosing groups (treatment groups A [low dose] and B

[high dose]) or 2 matched placebo plus SOC opioids (control treatment groups C or D) in a 2:2:1:1 ratio. Treatment group A (low dose) received intravenous acetaminophen doses ranging from 7.5 mg/kg for extreme preterm neonates to 12.5 mg/kg for infants. Treatment group B (high dose) received intravenous acetaminophen doses ranging from 10 mg/kg for extreme preterm neonates to 15 mg/kg for infants. Doses of acetaminophen or saline placebo were administered every 6 hours as a continuous intravenous infusion over 15 minutes for 4 doses.

All treatment groups had access to protocol-specified opioid rescue medication. After randomization, a certified, dedicated blinded assessor performed a pretreatment pain assessment using the Leuven Neonatal Pain Scale ([LNPS] in neonates and infants <6 months of age) or Face, Legs, Activity, Cry, and Consolability Scale ([FLACC] in infants ≥ 6 months to <24 months of age). A single dose of standard opioid was given 30 minutes prior to the planned start of study drug (T_0). Each subject then received 4 doses of the assigned study drug, 1 dose every 6 hours at T_0 , T_6 , T_{12} , and T_{18} , plus SOC opioids for 24 hours, and had protocol-specified assessments performed.

Blood samples were obtained at T_0 , $T_{0.5}$, T_2 , T_7 , and T_{12} , and urine samples were collected during the T_0 - T_6 range and the T_{18} - T_{24} range for PK analysis. Pain intensity assessments, LNPS or FLACC, were conducted at T_0 , $T_{0.5}$, T_1 , T_2 , T_3 , T_4 , T_6 , T_{12} , and T_{24} . Certara USA, Inc. performed population PK and PK-PD statistical analyses. Study completion assessments were performed 6 hours after the last dose of study drug, which included vital signs, physical examination, liver function tests, global evaluation of satisfaction with study treatment, and adverse event assessment.

The study's primary end point was total rescue opioid consumption (intravenous morphine equivalent) T_0 - T_{24} in each intravenous acetaminophen group and the combined placebo groups. Total opioid consumption over an 8-hour prerandomization qualification period initially was used to characterize a subject's consumption as either "low" or "high" based on a threshold hourly average value of 30 $\mu\text{g}/\text{kg}/\text{h}$ intravenous morphine equivalent (a total of 240 $\mu\text{g}/\text{kg}$ over 8 hours). During the study, a change was made to use a shorter time frame of 6 hours (with a total of 210 $\mu\text{g}/\text{kg}$ over 6 hours). As a result, stratification by prerandomization opioid consumption was no longer a factor and therefore excluded from the primary and secondary analyses. Secondary PK end points were area under the plasma concentration-time curve over the 6-hour dosing interval (AUC_{0-6}) to the last measurable concentration (AUC_{0-t}) and extrapolated to infinity ($\text{AUC}_{0-\infty}$), maximum plasma concentration (C_{max}), $t_{1/2}$, and clearance (CL), in addition to population PK and

Table 1. Subject Disposition by Age Category

	Intravenous Acetaminophen Groups			Control Groups			Total
	Group A	Group B	Group A+B	Group C	Group D	Group C+D	
Number of subjects randomized, total	66	72	138	35	42	77	215
Neonates	15	13	28	9	8	17	45
Younger infant	17	23	40	8	10	18	58
Intermediate-age infants	19	18	37	12	10	22	59
Older infants	15	18	33	6	14	20	53
Number of subjects completed, total (%)	52 (78.8)	55 (76.4)	107 (77.5)	26 (74.3)	26 (61.9)	52 (67.5)	159 (74.0)
Neonates	13 (86.7)	12 (92.3)	25 (89.3)	7 (77.8)	6 (75.0)	13 (76.5)	38 (84.4)
Younger infants	14 (82.4)	15 (65.2)	29 (72.5)	7 (87.5)	7 (70.0)	14 (77.8)	43 (74.1)
Intermediate-age infants	13 (68.4)	14 (77.8)	27 (73.0)	6 (50.0)	3 (30.0)	13 (59.1)	40 (67.8)
Older infants	12 (80.0)	14 (77.8)	26 (78.8)	6 (100.0)	6 (42.9)	12 (60.0)	38 (71.7)

PK-PD end points. The population PK analysis was performed using a 2-compartmental model with linear elimination, size effect on PK parameters and sigmoid maturation function on systemic CL. Post hoc PK parameters (AUC, C_{max} , V_{ss} , and $t_{1/2}$) were derived for individual subjects and summarized with descriptive statistics. PK-PD modeling was performed by including an effect compartment in the structural PK model.

Population PK analysis of acetaminophen in plasma was performed using a nonlinear mixed-effects modeling approach with NONMEM version VI. Dataset preparation, exploration, and visualization of the data, descriptive statistics, linear regression analysis, and survival PK-PD analyses were performed using R version 3.2. The programming library Perl-Speaks-NONMEM (PsN version 2.3.0) was used to evaluate and validate the model with a visual predictive check.

Results

The study was initiated in August 2012 and completed in August 2015, when the last enrolled subject completed the last assessment. A total of 215 subjects were randomized, with 66 in group A (low dose), 72 in group B (high dose), and 77 in group C+D (control group). Disposition of subjects by age category is summarized in Table 1.

Each participant who received any portion of study medication was included in the safety population ($n = 198$). The efficacy-evaluable population ($n = 197$) included subjects who received a dose of study drug and completed at least 1 assessment and was composed of 38 neonates, 54 younger infants, 55 intermediate-age infants, and 50 older infants. All patients were classified as surgical patients, and none had a traumatic injury. Demographic and baseline characteristics of subjects in the efficacy-evaluable population are presented in Table 2.

Among study participants, 186 subjects provided blood samples for analysis; 27 of these subjects had

results below the limits of quantification and were removed from the analysis. One subject was removed because of an unexpectedly high dose reported in the clinical data. As such, 158 subjects remained and were included in the PK analysis. Baseline demographics for these 158 subjects did not show significant deviation from the total study participants.

Population PK

From the 581 PK samples, a population PK analysis was done to fit concentration-time profiles of acetaminophen (Figure 1). Active group (group A+B) showed a biexponential disposition kinetics of acetaminophen. Residual (low) acetaminophen concentrations were observed in the combined placebo group (group C+D).

The population PK model was updated by combining 581 samples from the current study with the 1260 PK samples from pediatric subjects used in the previously developed intravenous acetaminophen population PK model. Typical values of the final population PK model are presented with the effect of arm (placebo control vs active) on CL and the reestimation of the constant describing age-related changes in CL (Table 3; Figure 2), along with the typical values derived with the previous model.

The final population PK model showed the individual predicted-versus-observed concentration plots were in good agreement (Figure 3). The population-predicted concentrations were clustered around the identity line.

The final population PK model was evaluated with a visual check of predicted concentration. This final model was very robust for predicting acetaminophen in 2 treatment arms (placebo and active). Thus, the model can be used to predict acetaminophen concentration and exposure in patients.

Individual post hoc acetaminophen PK parameters were derived for the neonate and infant populations,

Table 2. Summary of Demographics and Baseline Characteristics in the Efficacy Population

	Intravenous Acetaminophen Groups			Control Groups	Total, n = 197
	Group A, n = 61	Group B, n = 67	Group A+B, n = 128	Group C+D, n = 69	
Postnatal age (days)					
Mean (SD)	223.1 (175.2)	245.7 (208.7)	234.9 (193.0)	220.4 (175.1)	229.9 (186.6)
Median (min, max)	202.0 (2643)	187.0 (3725)	199.0 (2725)	194.0 (1664)	195.0 (1725)
Age categories, ¹ n (%)					
Neonates	13 (21.3)	12 (17.9)	25 (19.5)	13 (18.8)	38 (19.3)
Extreme preterm	0	2 (3.0)	2 (1.6)	1 (1.4)	3 (1.5)
Preterm	0	3 (4.5)	3 (2.3)	1 (1.4)	4 (2.0)
Full term	13 (21.3)	7 (10.4)	20 (15.6)	11 (15.9)	31 (15.7)
Younger infants	16 (26.2)	20 (29.9)	36 (28.1)	18 (26.1)	54 (27.4)
Intermediate age infants	18 (29.5)	17 (25.4)	35 (27.3)	20 (29.0)	55 (27.9)
Older infants	14 (23.0)	18 (26.9)	32 (25.0)	18 (26.1)	50 (25.4)
Sex, n (%)					
Male	44 (72.1)	40 (59.7)	84 (65.6)	43 (62.3)	127 (64.5)
Female	17 (27.9)	27 (40.3)	44 (34.4)	26 (37.7)	70 (35.5)
Race, n (%)					
White	40 (65.6)	49 (73.1)	89 (69.5)	46 (66.7)	135 (68.5)
Black or African American	12 (19.7)	9 (13.4)	21 (16.4)	9 (13.0)	30 (15.2)
American Indian or Alaska Native	1 (1.6)	0	1 (0.8)	0	1 (0.5)
Asian	3 (4.9)	4 (6.0)	7 (5.5)	6 (8.7)	13 (6.6)
Other	4 (6.6)	4 (6.0)	8 (6.3)	5 (7.2)	13 (6.6)
Missing	1 (1.6)	1 (1.5)	2 (1.6)	3 (4.3)	5 (2.5)
Weight at screening (kg)					
Mean (SD)	6.97 (2.79)	6.96 (3.05)	6.96 (2.92)	6.96 (2.69)	6.96 (2.83)
Median (min, max)	6.75 (2.6, 13.7)	7.00 (1.0, 14.3)	7.00 (1.0, 14.3)	7.10 (0.8, 12.0)	7.00 (0.8, 14.3)
Baseline opioid dose ($\mu\text{g}/\text{kg}$)					
Mean (SD)	45.9 (36.08)	49.7 (36.22)	47.9 (36.06)	47.2 (31.85)	47.6 (34.55)
Median (min, max)	48.3 (0, 170.5)	50.0 (0, 204.8)	50.0 (0, 204.8)	50.0 (0, 116.3)	50.0 (0, 204.8)

kg, kilogram; max, maximum; min, minimum; SD, standard deviation.

¹Subjects were divided into 4 age groups: neonates (<28 days), younger infants (28 days to <6 months), intermediate-age infants (6 months to <12 months), and older infants (12 months to <24 months). Neonates were further categorized into extreme preterm neonates (≥ 28 to <32 weeks' gestational age), preterm neonates (≥ 32 to <37 weeks' gestational age), and full-term neonates (≥ 37 weeks to ≤ 40 weeks' gestational age).

and the precision of the PK parameters was deemed acceptable. Subsequently, a comparability study was conducted between the PK parameter and exposure levels data derived from the neonate and infant populations with similar data gathered from the adult population from a prior study. The results of these 2 sets of data for intravenous acetaminophen and the PK parameters after the first dose of intravenous acetaminophen are shown below (Table 4). Median half-life of acetaminophen in neonates and younger infants ranged between 3.2–3.4 and 2.7 hours, respectively, which is 1.2-fold to 1.5-fold the median in adults (2.33 hours). The median half-life for intermediate and older infants was similar to that of adults. The median acetaminophen CL adjusted for body weight in neonates (0.19–0.22 L/h/kg) was slightly lower than that observed in adult subjects (0.28 L/h/kg). However, median weight-adjusted CL in infants (range, 0.30–0.37 L/h/kg) was slightly higher than in adults (0.278 L/h/kg). Median acetaminophen V_{ss} in infant and neonate patients ranged from 0.85 to 0.95 L/kg, which was slightly higher than that observed in adults (0.80 L/kg). Median C_{max}

values in both neonate dosing cohorts were slightly lower than those observed in infants and adults. The higher dosing cohorts had higher median C_{max} for the infant subgroups compared with median values observed in adults (ie, 26.7, 29.1, and 27.9 $\mu\text{g}/\text{mL}$ in younger, intermediate, and older infants, respectively, compared with 24.7 $\mu\text{g}/\text{mL}$ in adults given 1000 mg every 6 hours). At low-dose levels, neonates and younger infants showed higher median AUC_{τ} than that observed in intermediate and older infants, with 26% and 28% higher values in neonates and younger infants, respectively, compared with older infants. At higher-dose levels, median AUC_{τ} values were within 10% of the median observed in adults who received 1000 mg every 6 hours (40.5 $\mu\text{g}\cdot\text{h}/\text{mL}$), with the exception of the median in extreme preterm neonates, which was approximately 32% lower. The data for this subgroup should be interpreted with caution given the small sample size of only 2 patients. The majority of subjects included in the new analysis was from 40 to 143 weeks of postmenstrual age (ie, ~ 0 to 2 years old), whereas the Palmer study included 50 patients aged from 33.7

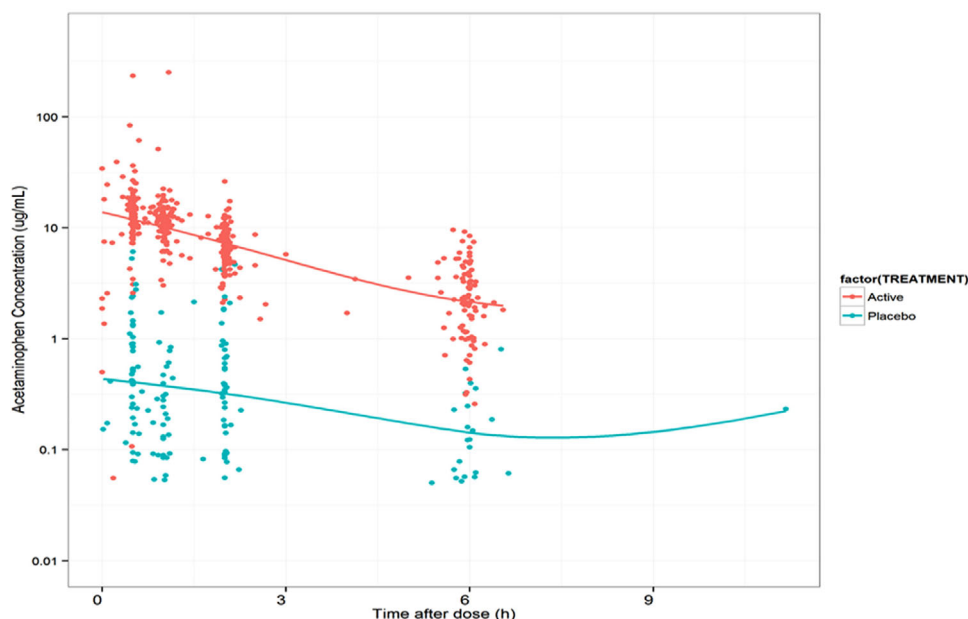


Figure 1. Population PK concentration-time profiles for acetaminophen. Lines represent locally weighted scatter smoothing (LOESS).

Table 3. Typical Acetaminophen Values of Final Population PK Model

Parameters	Current Model	Previous Model
Population model		
CL (L/h)	$18.9 \times \left(\frac{WT}{70}\right)^{0.75}$	$18.4 \times \left(\frac{WT}{70}\right)^{0.75}$
Placebo on CL	$\times 0.524$	
Maturation function	$\times \left[\exp\left(-\left(PMA - 40\right) \times \frac{\ln(2)}{32.6^*}\right) \right]$	$\times \left[\exp\left(-\left(PMA - 40\right) \times \frac{\ln(2)}{41.0}\right) \right]$
V_c (L)	$23.0 \times \left(\frac{WT}{70}\right)$	$16.0 \times \left(\frac{WT}{70}\right)$
CL _p (L/h)	$47.7 \times \left(\frac{WT}{70}\right)^{0.75}$	$97.8 \times \left(\frac{WT}{70}\right)^{0.75}$
V_p (L)	$45.5 \times \left(\frac{WT}{70}\right)$	$59.5 \times \left(\frac{WT}{70}\right)$
Individual variability		
ω^2_{CL}	0.127	0.14
ω^2_{Vc}	0.993	0.38
ω^2_{CLp}		0.0383
ω^2_{Vp}		0.0777
Residual variability		
Log residual error	0.221	
σ^2_{prop} (%)		27.9
σ^2_{add} (mg/L)		168.2

CL, systemic clearance; CL_p, intercompartmental clearance; PMA, postmenstrual age; PK, pharmacokinetic; V_c, volume of distribution of the central compartments; V_p, volume of distribution of the peripheral compartment; WT, body weight.

Note: in the current model, the correlation between CL and V_c BSV was 51.4%.

*Fixed at previous value derived in.

to 47.2 weeks of postmenstrual age, and Zuppa data included subjects aged from 41 to 906 weeks of postmenstrual age (~0 to 17 years old; Figure 4).

Efficacy

Total rescue opioid consumption was similar in groups A, B, or A+B compared with the combined placebo group (C+D). The primary efficacy result did not demonstrate a statistically significant reduction in the total rescue opioid consumption in each of the

individual intravenous acetaminophen groups (A or B) compared with the combined placebo group (C+D). Overall, none of the efficacy end points demonstrated significant differences in pain-related assessments between the intravenous acetaminophen treatment groups compared with the combined placebo groups.

PK-PD: Pain Intensity-by-Treatment Group

PK-PD modeling of pain intensity scores and time after last opioid consumption showed a decrease in pain

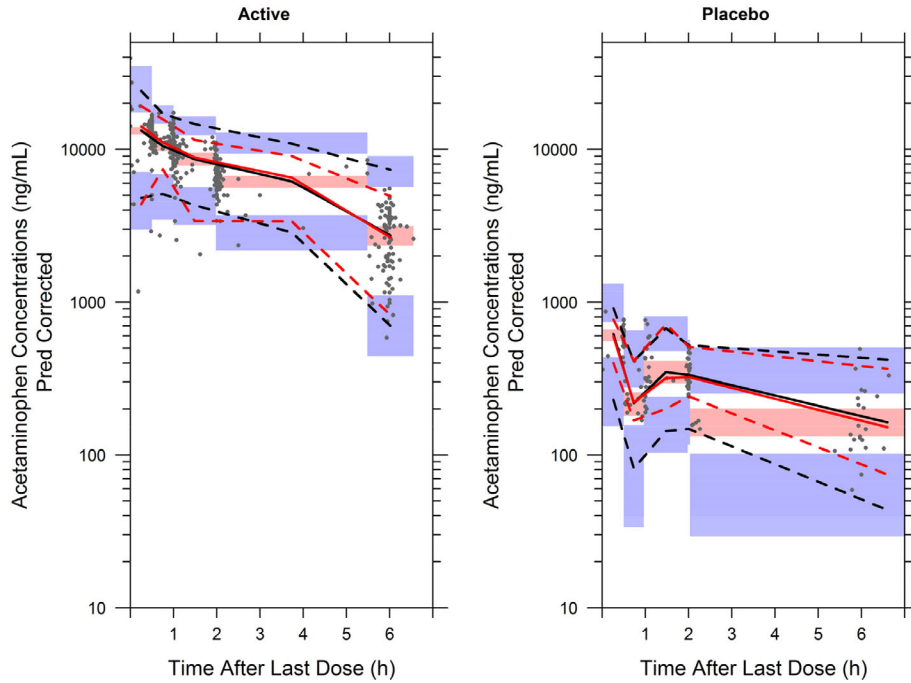


Figure 2. Visual predicted check — final population pk model.

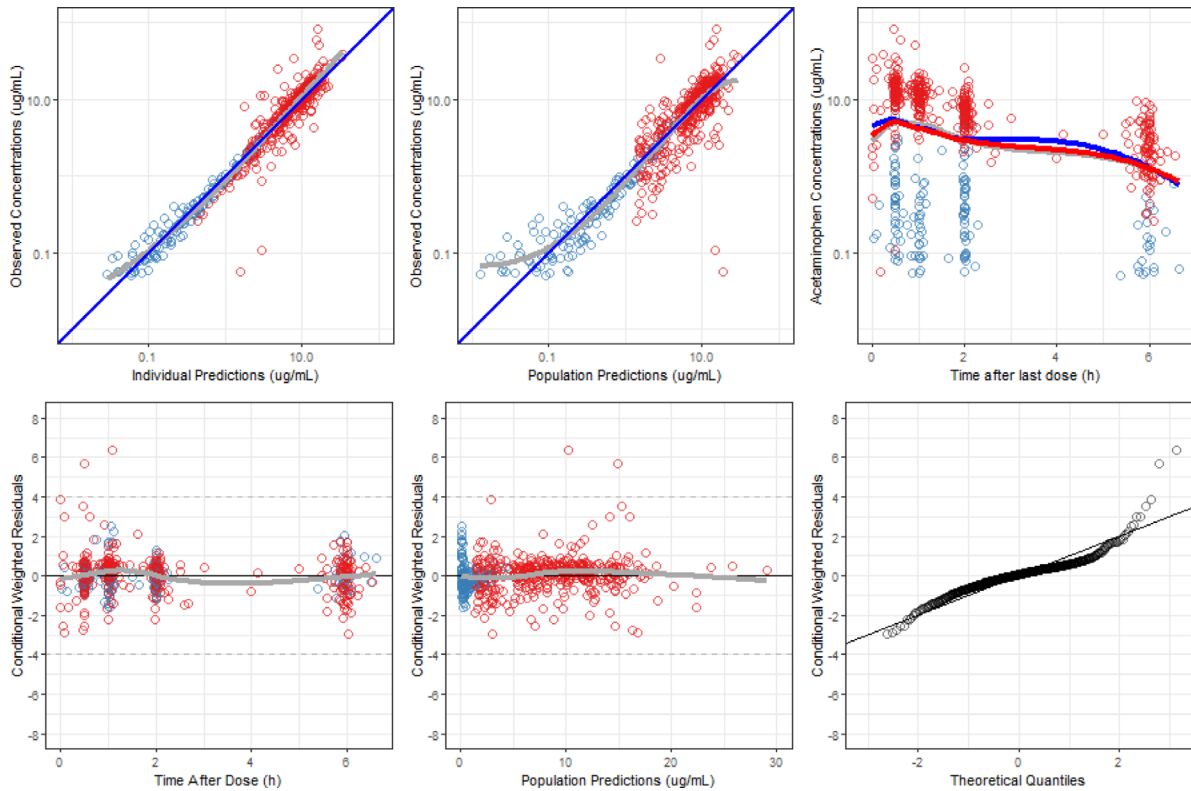


Figure 3. Final population PK model goodness of fit.

intensity in both groups 2–3 hours after the first dose of treatment (intravenous acetaminophen or placebo), followed by an increase. The increase in pain intensity scores occurred earlier in the placebo group.

PK-PD: Survival Analysis on Avoiding Opioid Rescue Medication

From approximately 2 to 20 hours, the percentage of subjects who were not taking rescue medication was

Table 4. Model-Derived PK Parameters of Intravenous Acetaminophen Before and After First Dose

Subpopulation	n	Prior to First Dose						After First Dose					
		CL			V _{ss}			Low-Dose Levels			High-Dose Levels		
		T _{1/2β} (h)	(L/h/kg)	(L/h)	(L/kg)	(L)	n	C _{max} (μg/mL)	AUC _τ (ug-hr/mL)	C _{max} (μg/mL)	AUC _τ (ug-hr/mL)		
Extreme preterm neonates	2	3.26 (0.26) 3.26	0.1921 (0.02314) 0.192	0.2377 (0.01184) 0.238	0.8485 (0.03485) 0.848	1.057 (0.1364) 1.06	High (10 mg/kg): n = 2	NA	NA	20.19 (6.259) 21.2	27.70 (8.092) 27.2		
Preterm neonates	2	3.08–3.45 3.23 (0.73)	0.176–0.208 0.2201 (0.08005)	0.229–0.246 0.4647 (0.1254)	0.824–0.873 0.9217 (0.1274)	0.960–1.15 1.968 (0.07839)	High (12.5 mg/kg): n = 2	NA	NA	22.82 (6.629) 22.8	43.24 (11.56) 43.2		
Full-term neonates	14	2.72–3.75 3.92 (2.6) 3.38	0.163–0.277 0.2231 (0.04910) 0.217	0.376–0.553 0.6991 (0.2957) 0.673	0.832–1.01 1.253 (1.281) 0.916	1.91–2.02 4.219 (5.567) 2.94	Low (10.0 mg/kg): n = 9	18.13 (4.330) 18.3	36.97 (8.325) 34.3	19.64 (11.66) 22.6	41.77 (22.27) 44.6		
Younger infants	34	2.77 (1.2) 2.71	0.3140 (0.08617) 0.299	1.723 (0.6719) 1.58	1.139 (0.7517) 0.948	6.13 (4.148) 5.65	High (12.5 mg/kg): n = 5	23.50 (7.144) 21.6	37.02 (10.43) 34.8	24.69 (9.466) 26.7	41.65 (13.82) 41.2		
Intermediate infants	31	2.35 (0.6) 2.29	0.3568 (0.1109) 0.336	3.009 (1.218) 2.46	0.9941 (0.2012) 0.926	8.339 (2.571) 7.50	Low (12.5 mg/kg): n = 14	20.76 (4.343) 20.8	30.19 (6.329) 30.0	30.01 (9.201) 29.1	45.52 (19.81) 41.6		
Older infants	31	2.21 (0.56) 2.15	0.4036 (0.09914) 0.368	4.108 (1.140) 3.83	1.128 (0.5686) 0.952	11.66 (7.020) 9.66	High (15.0 mg/kg): n = 17	20.19 (6.259) 21.2	27.70 (8.092) 27.2	27.07 (6.838) 27.9	38.76 (10.87) 38.7		
Adults	34	2.39 (0.57) 2.33	0.2678 (0.08236) 0.275	20.08 (5.808) 20.6	0.8330 (0.2238) 0.798	64.3 (12.55) 63.0	High (15.0 mg/kg): n = 18	NA	NA	28.39 (21.17) 24.7	42.48 (10.65) 40.5		
		(1.72–4.50)	(0.128–0.598)	(9.24–33.3)	(0.343–1.87)	(28.0–103)	6 hours			(11.8–139)	(25.5–72.4)		

AUC_τ, area under the concentration-time curve; CL, systemic clearance; C_{max}, maximum concentration; n, number of subjects; NA, not applicable; SD, standard deviation; T_{1/2β}, terminal elimination half-life; V_{ss}, total volume of distribution in steady state.
Mean (SD), median (minimum-maximum).

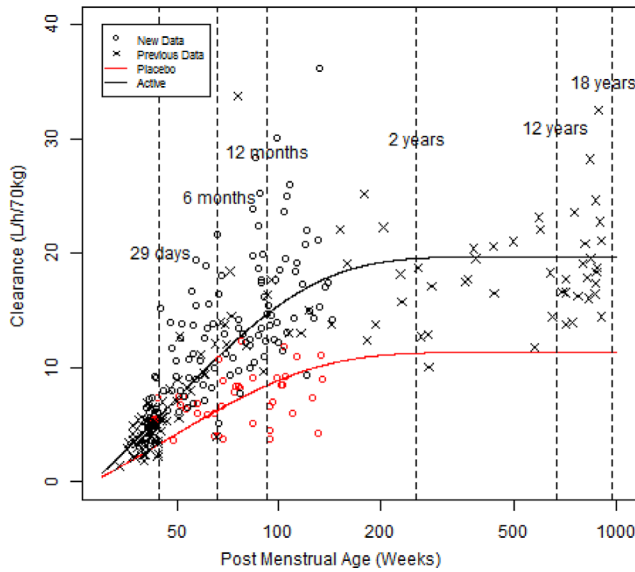


Figure 4. The relationship between clearance and postmenstrual age: a sigmoidal pattern with a clearance plateau of 18.9 L/h per 70 kg observed in neonates, infants, children, and adolescents.

higher in the combined intravenous acetaminophen active groups than in the combined placebo groups. Of note, the active group with both low and high preredomization opioid consumption showed a higher probability of avoiding rescue medication compared with the corresponding placebo group, and the separation between active and placebo groups with high preredomization opioid consumption was greater (Figure 5). Notably, the probability of avoiding rescue medication was significantly higher in patients with acetaminophen AUC_{0-6} values greater than $42.8 \mu\text{g}\cdot\text{h/mL}$ ($P < .05$).

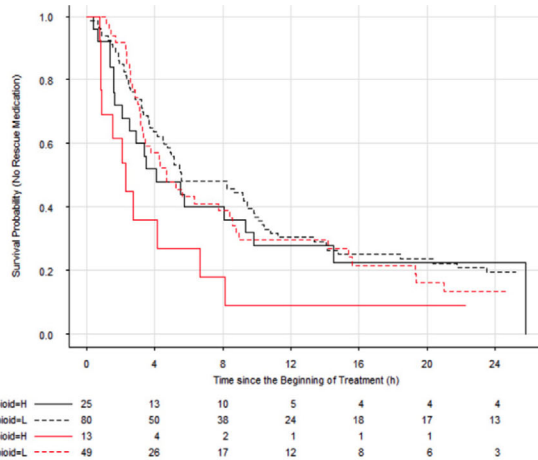


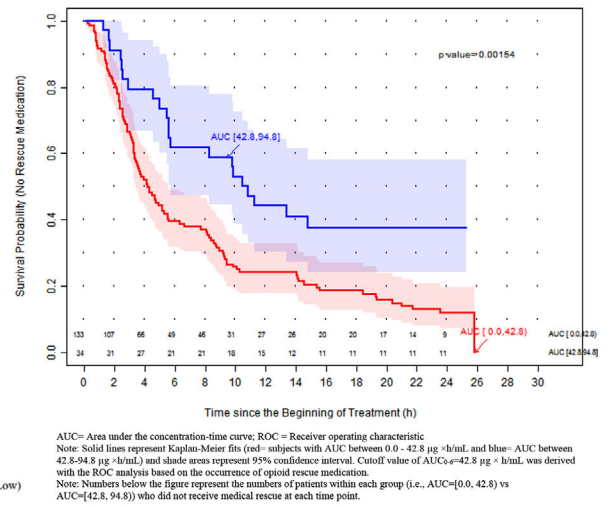
Figure 5. Probability of avoiding opioid rescue medication versus time — active (intravenous acetaminophen) versus placebo groups by preredomization opioid level.

PK-PD: Linear Regression Analysis of AUC and Rescue Opioids

Linear regression of the relationship between AUCs and rescue opioids on different treatment intervals showed a negative and non-statistically significant relationship for 0–6, 0–12, and 0–18 hours (Figure 6A). Concentrations in the effect compartment (C_{eff}) were derived with the equilibration half-life fixed to the value estimated.³ Linear regression of the relationship between C_{eff} and pain score difference 1 hour post-dose showed small negative, non-statistically significant trends for FLACC. In addition, the relationship between total opioid consumption and PK exposure parameters and the correlation between acetaminophen concentration and pain intensity difference 1 hour postdose were performed (Figure 6B).

Safety

Physical examinations, vital signs, clinical laboratory tests including liver function tests, and treatment-emergent adverse events (TEAEs) were used to assess safety. No deaths resulting from TEAEs occurred during this study. A total of 3 subjects experienced serious adverse events of whom 2 were treatment emergent: 1 in the combined control treatment group (leukocytosis) and 1 in intravenous acetaminophen treatment group B (apnea). Significantly fewer subjects in group B (32.8%) experienced at least 1 TEAE ($P = .010$) compared with the combined placebo groups (55.7%). In addition, significantly fewer subjects in groups A and B prematurely discontinued the because of a TEAE when compared with the combined placebo groups ($P = 0$ and $P = .009$, respectively). Liver function tests measured through alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzyme levels showed that no



AUC= Area under the concentration-time curve; ROC = Receiver operating characteristic
 Note: Solid lines represent Kaplan-Meier fits (red= subjects with AUC between 0.0 - 42.8 $\mu\text{g}\cdot\text{h/mL}$ and blue= AUC between 42.8-94.8 $\mu\text{g}\cdot\text{h/mL}$) and shade areas represent 95% confidence interval. Cutoff value of $AUC_{0-6}=42.8 \mu\text{g}\cdot\text{h/mL}$ was derived with the ROC analysis based on the occurrence of opioid rescue medication.
 Note: Numbers below the figure represent the numbers of patients within each group (i.e., AUC=(0.0, 42.8) vs AUC=(42.8, 94.8) who did not receive medical rescue at each time point.

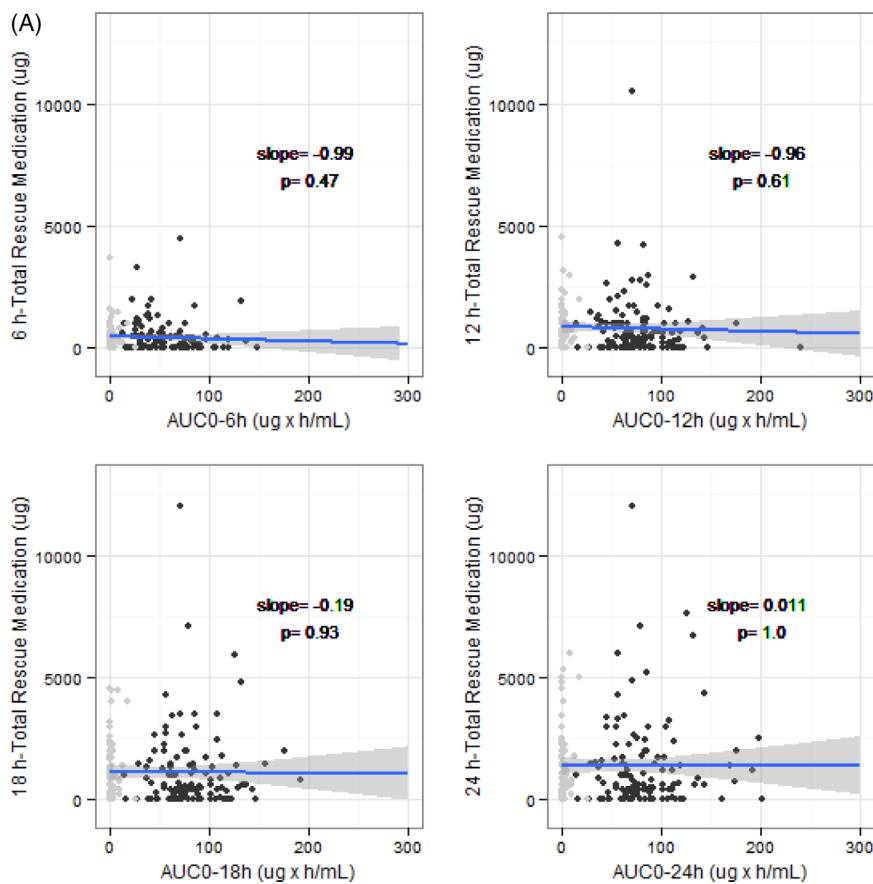


Figure 6. (A) Relationship between total opioid rescue medication and different treatment intervals (ie, 0–6, 0–12, 0–18, and 0–24 hours) with linear regression results. (B) Relationship between and pain intensity difference 1 hour postdose and concentration of acetaminophen in plasma/blood and effect compartments 1 hour postdose with linear regression results by score scale.

subject in any group had an ALT postbaseline value $> 3 \times$ the upper limit of normal (ULN); however, 4 subjects in the combined placebo group and 1 subject each in group A and group B had an AST postbaseline value $> 3 \times$ ULN. No subject had a postbaseline ALT or AST value $> 5 \times$ ULN.

Discussion

We performed a randomized, placebo-controlled study of intravenous acetaminophen in neonate and infant patients with acute postoperative pain to assess PK, PD, efficacy, and safety of repeated doses administered over 24 hours. Pharmacokinetic modeling results from this study indicate that acetaminophen PK and exposure levels in neonates receiving intravenous acetaminophen 12.5 mg/kg and in infants receiving 15 mg/kg are comparable to the exposure levels in adults receiving 1000 mg every 6 hours. This served as the basis for revised dosing recommendations for the treatment of fever in neonates (≥ 32 weeks' gestational age; no dosing recommendations are provided for neonates < 32 weeks' gestational age) and infants provided in

the updated 2017 Ofirmev (acetaminophen) injection prescribing information. For neonates, including premature neonates born ≥ 32 weeks' gestational age up to 28 days' chronological age, the dosing recommendations are 12.5 mg/kg every 6 hours to a maximum daily dose of acetaminophen of 50 mg/kg/day, with a minimum dosing interval of 6 hours. For infants 29 days to 2 years of age, the dosing recommendations are 15 mg/kg every 6 hours to a maximum daily dose of acetaminophen of 60 mg/kg/day, with a minimum dosing interval of 6 hours. Inferences can be made on the findings from this study with healthy adult patients who received a 1000-mg dose every 6 hours (data not published).

Consistent with the current study, prior PK studies demonstrated exposure of intravenous acetaminophen in children and adolescents was similar to adults, but higher in neonates and infants.^{1,2} Population PK modeling of data from these 2 studies — updated to include data from the current study — demonstrated that PK parameters in neonates and infants were comparable to those in older populations by compensating for both significantly decreased CL and longer $t_{1/2}$.

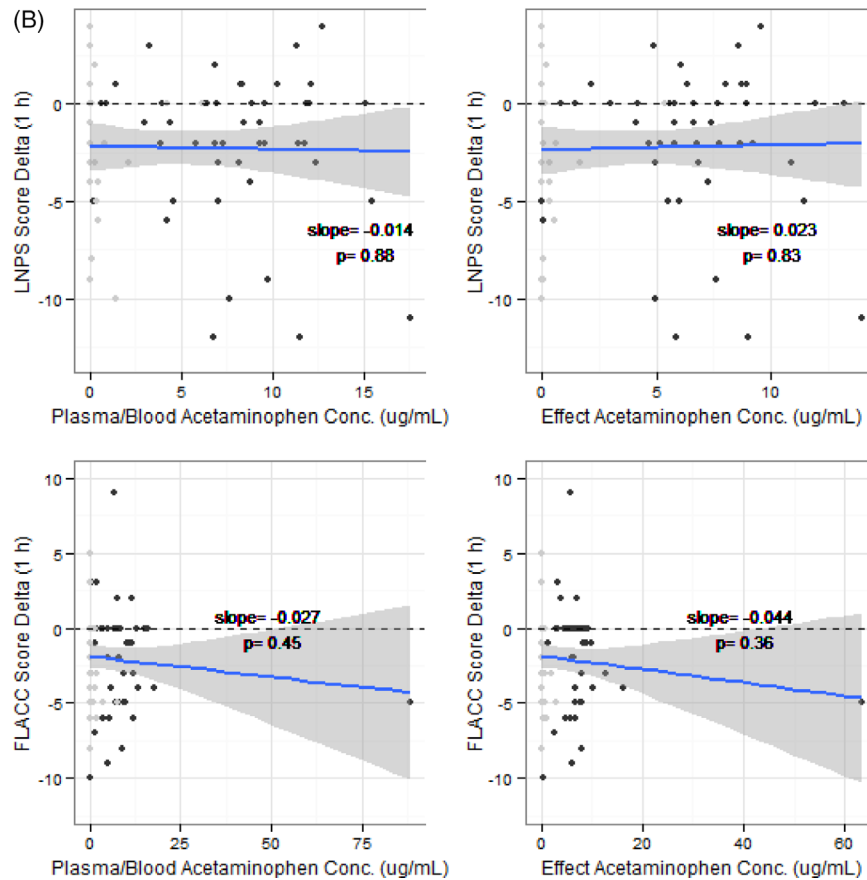


Figure 6. Continued.

To characterize the variation in PK of acetaminophen across the human age span, Wang and colleagues performed a population PK meta-analysis using data from 8 clinical studies of preterm neonates to adults, with a specific focus on clearance.⁴ Acetaminophen was administered intravenously in 6 of the studies and PR in 2 of the studies. Concentration-time data obtained in 220 neonates (postnatal age 1–76 days, gestational age 27–42 weeks), infants (0.11–1.33 years), children (2–7 years), and adults (19–34 years) were analyzed using NONMEM 7.2. In the covariate analysis, linear functions, power functions, and a power function with a body weight-dependent exponent were tested. A PK model for characterizing changes in acetaminophen PK parameters across the pediatric age range was developed. Clearance was found to change in a nonlinear manner with body weight. Based on the final model, dosing guidelines were proposed from preterm neonates to adolescents, resulting in similar exposure across all age ranges. For individuals from 40 days to 7 years of age with body weight between 7 and 20 kg, the model by Zuppa and colleagues and in the current study estimated slightly greater clearance compared with the estimates by Wang and colleagues.

Cook and colleagues sought to develop a population PK model for intravenous acetaminophen in preterm and term neonates and to assess the generalizability of the model by testing its predictive performance in an external data set.⁵ Nonlinear mixed-effects models were constructed from acetaminophen concentration-time data in NONMEM 7.2. Potential covariates included body weight, gestational age, postnatal age, postmenstrual age, sex, race, total bilirubin, and estimated glomerular filtration rate. An external data set was used to test the predictive performance of the model through calculation of bias, precision, and normalized prediction distribution errors. The model-building data set included 260 observations from 35 neonates with a mean gestational age \pm standard deviation (SD) of 33.6 ± 6.6 weeks. A 1-compartment model with first-order elimination was used to describe the data. Body weight predicted acetaminophen CL and volume of distribution, which were estimated as 0.35 L/h (5.5% relative standard error; 30.8% coefficient of variation) and 2.46 L (3.5% relative standard error; 14.3% coefficient of variation), respectively, at the mean subject weight of 2.30 kg. An external evaluation was performed on an independent data set that included 436 observations from 60 neonates with a mean

gestational age \pm SD of 35.6 ± 4.3 weeks, the median prediction error was 10.1% (95% confidence interval [CI], 6.1%–14.3%), and the median absolute prediction error was 25.3% (95%CI, 23.1%–28.1%). The authors concluded that weight predicted intravenous acetaminophen PK in neonates ranging from extreme preterm to full-term gestational status; external evaluation suggested that these findings should be generalizable to other similar patient populations.

Several differences were noted between the study by Cook and colleagues and the current study. Importantly, the dosing regimens were very different in the 2 studies, with Cook and colleagues using higher doses (15 mg/kg versus 10 mg/kg in extreme preterm, preterm, and full-term infants) and a longer dosing infusion time (30 versus 15 minutes). Also, Cook and colleagues claimed a 1-compartment model is more accurate than the 2-compartment model used in the current study, which may be because of the sparseness of the data collected in neonates to evaluate the biphasic elimination. Cook and colleagues only evaluated neonates, and thus for this group they had more subjects and samples and greater ethnic diversity. Although Cook and colleagues showed slightly lower CL than the current study, the U.S. Food and Drug Administration did not express concern regarding the neonate and young infant dosing recommendations proposed and now included in the 2017 Ofirmev (acetaminophen) injection prescribing information, which is consistent with results from our study.

Although not demonstrated in the current study, the efficacy of intravenous acetaminophen for postoperative pain management in neonates and infants was shown in 2 prior studies.^{6,7} In the study by Allegaert and colleagues, significant improvement in pain score ($P < .02$) was seen within 30 minutes of administration of intravenous acetaminophen. In the study by Ceelie and colleagues, pediatric patients who received intravenous acetaminophen used significantly less morphine in the first 48 hours postoperatively than those receiving morphine. In the current study, although significant differences were not seen in pain-related assessments between the intravenous acetaminophen and placebo groups, the subset of patients in the intravenous acetaminophen group with lower prerandomization opioid consumption showed a higher probability of avoiding rescue medication compared with placebo. This result should be interpreted with caution given that during the study the protocol was amended to alter the threshold for prerandomization opioid consumption level (low or high). Subjects previously classified as having either low or high opioid consumption were not reassigned based on the new threshold. On study, all subjects received an opioid dose (full loading dose or lesser amount, based on the subject's pain score) within

30 minutes of the planned first dose of study medication. Further studies are needed to fully characterize the efficacy of intravenous acetaminophen for pain management, including impact on opioid consumption, in this patient population.

Conclusion

Intravenous acetaminophen population PK modeling demonstrated that neonates receiving 12.5 mg/kg every 6 hours show a PK profile similar to younger, intermediate, and older infants, adolescents, and adults weighing <50 kg receiving 15 mg/kg every 6 hours and adults weighing \geq 50 kg receiving 1000 mg every 6 hours.

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Conflicts of Interest

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Data Accessibility Statement

This trial is registered at <https://ClinicalTrials.gov> (NCT01635101). The data presented in this article are not publicly available. Requests for additional information should be made to the corresponding author.

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