


SHORT REPORT

Pharmacokinetics of ticarcillin–clavulanate in premature infants

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Ticarcillin–clavulanate covers a broad spectrum of pathogens that are common in premature infants. In infants <30 weeks gestational age, pharmacokinetic data to guide ticarcillin–clavulanate dosing are lacking. We enrolled 15 premature infants <30 weeks gestational age, determined pharmacokinetic parameters, and performed dosing simulations to determine optimal dosing for ticarcillin–clavulanate. The infants had a median (range) postnatal age (PNA) of 18 days (6–44 days) and gestational age of 25 weeks (23–28 weeks). Clearance was lower in infants with a PNA <14 days (0.050 L/kg/h [range 0.043–0.075]) compared with a PNA ≥14–45 days (0.078 L/kg/h [0.047–0.100]), consistent with maturation of renal function. Dosing simulations determined that ticarcillin 75 mg/kg q12h (PNA <14 days) or q8h (PNA ≥ 14–45 days) achieved the target exposure for organisms with a minimum inhibitory concentration ≤16 µg/mL in >90% of simulated infants. For highly resistant organisms (minimum inhibitory concentration 32 µg/mL), increased dosing frequency or extended infusion are necessary.

KEYWORDS

clavulanate, infants, pharmacokinetics, premature, ticarcillin

1 | INTRODUCTION

Seventy percent of late-onset sepsis in the neonatal intensive care unit is due to Gram-positive organisms.¹ Coagulase-negative *Staphylococcus* is the most commonly isolated pathogen,^{1,2} and *Staphylococcus aureus* is the second most common.^{2–7} Infants with these infections have prolonged hospitalizations and an increased risk of neurodevelopmental impairment and death.^{2,8–14}

Ticarcillin–clavulanate covers a broad spectrum of pathogens, including methicillin-sensitive *Staphylococcus aureus*, coagulase-

negative *Staphylococcus* species, and many Gram-negative bacteria.¹⁵ Ticarcillin–clavulanate is primarily eliminated unchanged via the kidneys, and clearance (CL) in infants will be impacted by maturation of renal function. Maturation-related change in ticarcillin–clavulanate CL is supported by PK studies in premature and term infants where CL increased with postnatal age (PNA) and gestational age (GA).^{16–21} Of note, only 3 infants in the above studies were < 30 weeks GA at birth.

The pharmacodynamic (PD) target for β-lactam efficacy is the fraction of time the concentration of unbound drug remains above the minimum inhibitory concentration (fT > MIC). For β-lactam drugs, bactericidal effects in adults are achieved with 50% fT > MIC.^{22,23} However, a target of 75% fT > MIC has been proposed in premature infants due to their immunocompromised state.^{24,25} The goal of this study was

PI statement: The authors confirm that the Principal Investigator for this paper is P. Brian Smith and that he has direct clinical responsibility for patients.

to characterize the PK of ticarcillin in premature infants <30 weeks GA and perform simulations to identify the optimal dose in this population.

2 | METHODS

2.1 | Participant population

Pharmacokinetic (PK) samples were obtained from a multicentre, prospective PK study of the antistaphylococcal agents clindamycin, rifampin and ticarcillin–clavulanate in infants (Clinicaltrials.gov #NCT01728363; IND #115,396). The ticarcillin–clavulanate cohort enrolled premature infants (PNA <91 days; GA <30 weeks) with normal renal function and suspected or confirmed infection. Complete inclusion/exclusion criteria can be found on ClinicalTrials.gov. The study protocol was reviewed and approved by the institutional review board of each participating institution.

2.2 | Drug dosing and sample collection

Ticarcillin–clavulanate dosing was based on the ticarcillin component at 75 mg/kg infused over 30 minutes. Dosing frequency was determined based on PNA, with PNA <14 days administered every 12 hours and PNA ≥ 14–45 days administered every 8 hours. The local standard-of-care dose could be administered if the site principal investigator deemed it appropriate. Up to 7 optimally timed plasma PK samples were collected after dose 3, 4, 5 or 6.

2.3 | Analytical methods

Total ticarcillin concentrations in plasma were quantified using a validated HPLC/MS/MS assay. Accuracy and precision were within the Food and Drug Administration bioanalytical assay validation criteria (e.g. ±15%).²⁶ The lower limit of quantification was 500 ng/mL (see supplementary materials for details).

2.4 | Population pharmacokinetic analysis

Because ticarcillin–clavulanate is supplied in a 30:1 fixed ratio and dosing is based on ticarcillin component, PK analysis focused on ticarcillin. Ticarcillin plasma PK data were analysed with a nonlinear mixed effects modelling approach using NONMEM (version 7.2, Icon Solutions, Ellicott City, MD, USA). The first-order conditional estimation method with interaction was used for all model runs. Data manipulation and visualization were performed using STATA 15 (College Station, TX, USA).

One- and two-compartment PK models were explored with assumed linear PK.²⁷ Between-subject variability was assessed for PK model parameters using an exponential relationship. Both diagonal and block Omega matrices for covariance were explored. Proportional, additive and combined (additive plus proportional) residual error models were explored. Body weight (WT) was assumed to be a significant covariate for CL and volume of distribution (V) and was included

What is already known about this subject

- Infection is common in premature infants and results in substantial morbidity and mortality.
- Ticarcillin–clavulanate covers the most common pathogens in premature infants, but appropriate dosing in premature infants <30 weeks gestational age is unknown.

What this study adds

- This pharmacokinetic trial of ticarcillin–clavulanate enrolled 15 premature infants <30 weeks gestational age.
- Clearance increased with postnatal age (PNA) and gestational age, reflecting maturation of renal function.
- Ticarcillin 75 mg/kg q12h (PNA < 14 days) or q8h (PNA ≥ 14–45 days) achieved the target exposure for common organisms. For highly resistant organisms, increased dosing frequency or prolonged infusion are necessary.

in the base model. The relationship between WT and PK parameters was allometrically characterized using a fixed exponent (0.75 and 1) for CL and V parameters, respectively.

Other covariates were tested for model inclusion based on physiological relevance and by visual inspection of scatter and box plots of the individual deviations from the population-typical value PK parameters (etas) against covariates. The covariates explored were postmenstrual age (PMA), PNA, serum creatinine (SCR), total bilirubin, serum albumin, haematocrit, race, ethnicity and sex. The relationship between age and CL was also explored using a sigmoidal maximum efficacy (E_{max}) maturation function as shown in equation 1. As a measure of age, PNA and PMA were explored.

$$F_{age} = \frac{age^{Hill}}{TM_{50}^{Hill} + age^{Hill}} \quad (1)$$

where F_{age} denotes the fraction of the adult CL value; TM_{50} represents the value of age (days for PNA and weeks for PMA) when 50% adult CL is reached; and $Hill$ (Hill coefficient) is a slope parameter for the sigmoidal maturation model. This relationship was first tested by estimating TM_{50} and $Hill$ and then by fixing TM_{50} to 47.7 weeks and $Hill$ to 3.4, values representing maturation of glomerular filtration in infants.²⁸

With the exception of WT, other continuous covariates were normalized to the population median value. A forward inclusion ($p < .05$) and backward elimination ($p < .01$) approach was used to evaluate statistical significance.

2.5 | Population PK model evaluation and validation

During the model-building process, successful minimization, diagnostic plots, plausibility and precision of parameter estimates, as well as objective function value (OFV) and shrinkage values were used to assess model appropriateness. Parameter precision for the final model was evaluated using non-parametric bootstrapping (1000 replicates) to generate the 95% confidence intervals for parameter estimates. A visual predictive check (VPC) was performed, whereby the final model was used to generate 1000 Monte-Carlo simulation replicates per time point of ticarcillin exposure. The number of observed concentrations outside of the 90% prediction interval for each time point was quantified.

2.6 | Dose–exposure evaluation

Multiple dosing regimens were evaluated using Monte-Carlo simulations based on PK parameters and associated variability generated from the final ticarcillin PK model (Table S1). We evaluated the regimen used in the current trial (referred to as Pediatric Trials Network [PTN]); the PTN regimen with increased frequency (PTN-increased frequency); the PTN regimen with extended infusion durations (PTN-extended infusion); as well as regimens from common dosing guidelines (Harriet Lane, Neofax).^{29,30}

A population of 1000 virtual premature (GA <30 weeks) infants was generated using PK-Sim® (version 5.3.2; Bayer Technology Services GmbH, Leverkusen, Germany) population builder.³¹ Each simulated infant was assigned an SCR value. SCR values (mg/dL) were determined using the “rnormal” function in STATA from the

following distributions centred around the mean (standard deviation): PNA <3 days: SCR 1.1 (0.06); PNA 3 to < 15 days: SCR 0.7 (0.06); PNA 15 to < 22 days: SCR 0.6 (0.05); and PNA 22–45 days: SCR 0.4 (0.03).³² The demographics and distributions of SCR values were comparable between the study population and the simulated population.

To assess the number of infants who achieved the surrogate PD target of efficacy, concentration of unbound drug (fC) was calculated assuming the fraction unbound to be 55%.¹⁵ Unbound concentrations at 75% of the dosing interval at steady state (fC_{75ss}) were calculated. The probability of fC_{75ss} of ticarcillin exceeding different MIC levels was determined and plotted against MICs. Maximum plasma concentration (C_{MAX}) was used as a surrogate for safety and values were comparable to adult C_{MAX} values (218–333 $\mu\text{g}/\text{mL}$) after doses that showed favourable safety.^{33–35} Optimal ticarcillin dosing was selected when >90% of infants achieved therapeutic exposures.

3 | RESULTS

3.1 | Participant baseline characteristics

Fifteen participants from 2 centres were enrolled (Table 1) and contributed 65 PK samples. The median (range) ticarcillin dose was 75 mg/kg (70–81). Pharmacokinetics sampling began after 3 (2–5) doses. The number of samples collected per participant was 5 (3–6). No ticarcillin concentrations were below the quantitation limit.

TABLE 1 Clinical characteristics

Variable	Median (range) or n (%)		
	Postnatal age < 14 d	Postnatal age 14–45 d	All
<i>n</i>	5	10	15
Gestational age (weeks)	25 (24–28)	26 (23–28)	25 (23–28)
Postnatal age (d)	7 (6–10)	23 (14–44)	18 (6–44)
Postmenstrual age (weeks)	26.0 (24.9–29.3)	29.4 (26.0–31.7)	29.3 (24.9–31.7)
Body weight (kg)	0.68 (0.56–1.01)	0.92 (0.59–1.22)	0.83 (0.56–1.22)
Female	2 (40)	2 (20)	4 (27)
Race			
White	-	1 (10)	1 (7)
Black or African American	5 (100)	9 (90)	14 (93)
Ethnicity			
Hispanic or Latino	-	1 (10)	1 (7)
Not Hispanic or Latino	5 (100)	8 (80)	13 (86)
Not reported	-	1 (10)	1 (7)
Laboratory values			
Serum creatinine (mg/dL)	0.8 (0.4–1.3)	0.4 (0.3–0.9)	0.5 (0.3–1.3)
Serum albumin (g/dL)	3.0 (3.0–3.5)	2.9 (2.2–3.4)	3.0 (2.2–3.5)

3.2 | Population pharmacokinetics model development

A 1-compartment PK model characterized the ticarcillin data well (Figure S1, S2). Estimates of between-subject variability on V (etaV) resulted in high residual standard error and shrinkage; etaV was consequently fixed at zero.

On univariable analysis, incorporation of PMA on CL resulted in the largest drop in the OFV (−17.19), followed closely by a sigmoidal maturation function on CL using PMA and fixing TM_{50} and the Hill coefficient at 47.7 weeks and 3.4, respectively (−17.045). Other covariates that resulted in significant drops in the OFV for ticarcillin were PNA on CL (−10.11) and SCR on CL (−8.562). In the ticarcillin multivariable analysis, SCR was tested with PNA- and PMA-based models and was retained in both models in the backward elimination step. The PMA-based maturation function with SCR on CL was chosen as the final model because it resulted in the largest drop in the OFV and was determined to be more generalizable due to its physiological relevance.

Final model equations and parameter estimates are presented in Table 2. Individual empirical Bayesian *posthoc* parameter estimates showed that CL was lower in infants with a PNA <14 days with median (range) 0.050 L/kg/h (0.043–0.075) compared with a PNA ≥14–45 days with 0.078 L/kg/h (0.047–0.100). Median CL for the overall population was 0.074 L/kg/h (0.043–0.100).

3.3 | Population pharmacokinetics model evaluation

Bootstrap analysis resulted in 96.2% of bootstrap datasets converging to >3 significant digits. The median of bootstrap fixed effects

parameter estimates were within 3.1% of population estimates from the original dataset for all parameters (Table 2). The VPC revealed a good fit between the observed and predicted concentrations with 95.4% (62/65) of observed ticarcillin concentrations falling within the 90% prediction interval.

3.4 | Dosing simulations

All of the simulated dosing regimens achieved an fC_{75ss} for 90% of simulated infants against organisms with an MIC distribution of 0.5–16 µg/mL (Figure 1, Table S2). Only the PTN-increased frequency regimen and the PTN-extended infusion regimen with at least a 2 hour infusion achieved the target for highly resistant organisms (MIC 32 µg/mL). Simulated ticarcillin steady-state C_{MAX} in infants for all regimens were comparable to or lower than mean measured ticarcillin C_{MAX} (218–333 µg/mL) in adults who tolerated a single 2–4g dose.^{33–35}

4 | DISCUSSION

The present study evaluated the population PK-PD of ticarcillin in a cohort of 15 premature infants <30 weeks GA at birth with suspected serious infection. After accounting for weight, age was the most important covariate for CL. A PMA-based sigmoidal maturation function resulted in a significant drop in OFV for ticarcillin CL. Because ticarcillin is renally eliminated, the PMA-based maturation function used values for Hill and TM_{50} that characterize maturation of glomerular filtration rate.^{28,36–38}

TABLE 2 Ticarcillin population pharmacokinetic equations and parameter estimates

Equations					
$CL = \theta_{CL} * \left(\frac{WT_i}{70}\right)^{0.75} * \left(\frac{PMA_i^{Hill}}{TM_{50}^{Hill} + PMA_i^{Hill}}\right) * \left(\frac{SCR}{0.5}\right)^{\theta_{CL-SCR}}$ $V = \theta_V * \left(\frac{WT_i}{70}\right)^1$					
Parameter	Estimate	RSE (%)	2.5 th percentile	Bootstrap ^a median	97.5 th percentile
Structural model					
θ_{CL} (L/h)	11.0	4.1	10.1	11.0	11.8
θ_V (L)	32.3	4.5	29.1	32.3	35.0
θ_{CL-SCR}	−0.257	35.5	−0.426	−0.265	−0.072
TM_{50} (weeks)	47.7 FIX	-	-	-	-
Hill	3.4 FIX	-	-	-	-
Between-subject variability					
CL (%CV)	11.5	51.9	2.6	10.8	16.7
V (%CV)	0 FIX	-	-	-	-
Residual error					
Proportional error (%)	21.0	26.0	14.9	20.7	25.6

CL, clearance; CV, coefficient of variation; Hill, Hill coefficient; RSE, relative standard error; SCR, serum creatinine; TM_{50} , age (weeks) when 50% adult clearance is reached; V, volume of distribution; V_{70KG} , volume of distribution (L) scaled to 70 kg; PNA, postnatal age.

^a1000 bootstrap runs were performed.

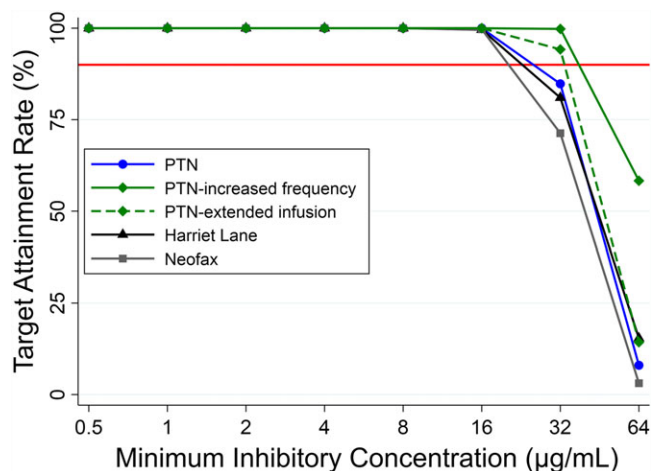


FIGURE 1 Target attainment rates for different ticarcillin dosing regimens for fraction of time the concentration of unbound drug remains above the minimum inhibitory concentration of 75%. Target attainment rate refers to the % of simulated infants who maintained an unbound ticarcillin concentration above the minimum inhibitory concentration for 75% of the dosing interval. The red horizontal line refers to a target attainment rate of 90%

Our estimate of CL in a standardized individual of 70 kg (11.0 L/h) was comparable to CL estimates reported in adults (6.7–9.2 L/h),^{33–35,39,40} showing that the maturation scaling worked well. Clearance estimates for the premature infants in the study population (0.074 L/kg/h) were higher than previously published CL estimates in premature infants with GA >30 weeks (0.047–0.067 L/kg/h)^{16,17} and lower than full-term infants and children (0.126–0.150 L/kg/h).^{20,21} These differences are probably due to a combination of PNA (median PNA in study population and other premature infants were 8 and 18 days, respectively) and the maturation of renal function.⁴¹ The population V estimate of ticarcillin in the study population (0.48 L/kg) was higher than estimates of V in premature infants >30 weeks GA (0.26–0.34 L/kg)^{16,17} and full-term infants and children (0.22–0.23 L/kg).^{20,21} The higher V in younger, more premature populations is probably multifactorial, including increased total body water⁴¹ and higher unbound fraction of drug^{42,43} compared to adults.

Based on the population PK model and simulations, the PTN, Harriet Lane²⁹ and Neofax,³⁰ dosing strategies met the overall goals for exposure against organisms commonly found in clinical practice with an MIC distribution of 0.5–16 µg/mL. However, these dosing regimens were suboptimal for highly resistant organisms (MIC >16 µg/mL). To treat highly resistant organisms, we recommend a different agent or increasing the dosing frequency of the PTN regimen. Our simulations assumed the fraction of unbound ticarcillin to be 55%.¹⁵ The unbound fraction may have been higher in our population because infants have lower concentrations of albumin and higher concentrations of endogenous substances (e.g., bilirubin) that can displace drugs from albumin-binding sites.^{42,43} Simulated ticarcillin steady-state C_{MAX} concentrations in infants were comparable to mean measured ticarcillin C_{MAX} in adults who tolerated a single 2–4g dose (218–333 µg/mL)^{33–35} and infants who tolerated a single dose of 83–100 mg/kg (159–447 µg/mL)¹⁷, suggesting a comparable safety profile.

In conclusion, for infants <30 weeks GA, we recommend a dose of 75 mg/kg infused over 30 minutes and dosed every 12 and 8 hours for PNA <14 and PNA 14–45 days, respectively.

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COMPETING INTERESTS

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CONTRIBUTORS

K.M.W., C.P.H., D.K.B. Jr., R.A., M.L., P.B.S., and M.C.W. all contributed to the design of the study, acquisition of data, and analysis and interpretation of results. S.J.B. contributed to the analysis and interpretation of results. G.M. and C.M.C. contributed to acquisition of data and interpretation of results. B.H. contributed to the design of the study and acquisition of data. All authors contributed to drafting and/or revising the manuscript and approved the final published version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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