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Short Communication

Population pharmacokinetics and dosing optimization of latamoxef in neonates and young infants

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ABSTRACT

Objectives: There has been recent renewed interest in historical antibiotics because of the increased antibiotic-resistant bacterial strains. Latamoxef, a semi-synthetic oxacephem antibiotic developed in 1980s, has recently been brought back into use for treatment of infections in newborns; however, it is still used off-label in neonatal clinical practice due to the lack of an evidence-based dosing regimen. This study was performed to evaluate the pharmacokinetics of latamoxef in neonates and young infants, and to provide an evidence-based dosing regimen for newborns based on developmental pharmacokinetics-pharmacodynamics (PK-PD).

Methods: Opportunistic blood samples from newborns treated with latamoxef were collected to determine the latamoxef concentration by high-performance liquid chromatography with UV detection. Population PK-PD analysis was conducted using NONMEM and R software. A total of 165 plasma samples from 128 newborns (postmenstrual age range 28.4–46.1 weeks) were available for analysis.

Results: A two-compartment model with first-order elimination showed the best fit with the data. Current body weight, birth weight, and postnatal age were identified as significant covariates influencing latamoxef clearance. Simulation indicated that the current dosing regimen (30 mg/kg q12h) is adequate with an MIC of 1 mg/L. For an MIC of 4 mg/L, 30 mg/kg q8h was required to achieve a target rate of 70% of patients having a free antimicrobial drug concentration exceeding the MIC during 70% of the dosing interval.

Conclusions: Based on the developmental PK-PD analysis of latamoxef, a rational dosing regimen of 30 mg/kg q12h or q8h was required in newborns, depending on the pathogen.

1. Introduction

Latamoxef (moxalactam) is a second-generation semi-synthetic oxacephem antibiotic that has been primarily used against Gram-positive and Gram-negative aerobic and anaerobic bacteria [1]. This drug has been used for treating adults, children, infants, and neonates since it was first introduced to clinical medicine in 1981 [2]. With the development of other novel antibiotics, using latamoxef for treating infectious diseases in newborns was reduced. However, as the prevalence of antibiotic-resistant bacterial strains has significantly increased, there has been recent renewed interest in historical antibiotics [3]. As a result, latamoxef has recently been brought back into use for treating bacterial infections in newborns.

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Because of excellent anti-microbial activity against most neonatal pathogens and the lack of serious adverse drug reaction, latamoxef has become an important choice for neonatal antibacterial treatment [2]. Although the history of latamoxef use in neonatal infectious diseases can be traced back to the 1980s, off-label use exists and pharmacokinetic (PK) data in newborns are limited in current clinical practice. Insufficient PK data often results in the use of inappropriate dosages, thereby increasing the failure rate of antimicrobial treatment and development of antibiotic resistance in pediatric cases [4]. Meanwhile, as developmental changes significantly influence the clearance and distribution of latamoxef, it is essential to establish a rational dosing regimen for newborns according to PK data [5].

To assess the PK features of latamoxef and develop a rational dosing scheme for newborns, this opportunity sampling-based population pharmacokinetics-pharmacodynamics (PK-PD) study was conducted.

2. Methods

A prospective, open-label latamoxef PK study was conducted at the neonatal intensive care units (NICUs) of the Beijing Children's Hospital and Beijing Obstetrics and Gynaecology Hospital. Opportunistic blood samples were obtained from the remaining blood, after blood gas or biochemical analysis, according to a previously approved method [6,7]. Plasma concentrations of latamoxef were determined using high-performance liquid chromatography by ultraviolet (UV) detection (HPLC-UV) as previously described [8]. Population PK-PD analysis was conducted using NONMEM (V 7.2), PsN (v2.30) and NPDE R package (v1.2) in a previous way [9,10]. MICs of 1 mg/L and 4 mg/L were used in the dosing regimen evaluation and optimization with Monte Carlo simulations. A detailed description of patients and methods is included in Supplementary materials.

3. Results

3.1. Characteristics of the study population

A total of 128 neonates and young infants were initially included in the study in 2017. The median gestational age at birth (GA) (standard deviation), postmenstrual age (PMA), and current weight (CW) of the 128 patients were 38.3 weeks (range 27.3–41.4), 39.7 weeks (range 28.4–46.1), and 3220.0 g (range 1000.0–4600.0), respectively (Supplementary Table 1).

3.2. Model building

For PK model building, 165 plasma concentrations of 128 newborns were available (range: < limit of quantification (LOQ)-196.2 μg/mL). There were 102 newborns with one sample and 26 newborns with two or more samples in this PK/PD study. Seventeen samples were lower than LOQ and half of LOQ value were used in PK modelling. The relationship between latamoxef concentration and time is shown in Supplementary Figure 1.

A two-compartment model using first-order elimination was employed for data fitting. The objective function values (OFV) and residual variability with a two-compartment model were less than those observed with a one-compartment model. The PK parameters of the model consisted of the distribution of the central volume (V_1), distribution of the peripheral volume (V_2), intercompartment clearance (Q), and clearance (CL) of latamoxef. Inter-individual variability was best expressed as an exponential model and then calculated for V_1 and CL. An exponential model optimally described residual variability.

Table 1
Population pharmacokinetic parameters of latamoxef and bootstrap results.

Parameters	Final model		Bootstrap	
	Final estimate	RSE (%)	Median	5^{th}–95^{th}
V_1 (L/kg)				
$V_1 = \theta 1 \times (CW/1955)$				
$\theta 1$	0.87	9.00	0.85	0.67–1.04
V_2 (L/kg)				
$V_2 = \theta 2 \times (CW/3220)$				
$\theta 2$	2.11	35.00	1.95	0.36–7.94
Q (L/h)				
$Q = \theta 3 \times (CW/3220)^{0.75}$				
$\theta 3$	0.03	27.10	0.03	0.01–0.08
CL (L/h)				
$CL = \theta 4 \times (CW/3220)^{0.75} \times F_{age}$				
$\theta 4$	0.27	6.40	0.27	0.24–0.31
$F_{age} = (BW/3100)^{\theta 5} \times (PNA/8)^{\theta 6}$				
$\theta 5$	0.29	37.80	0.32	0.12–0.57
$\theta 6$	0.21	18.30	0.22	0.12–0.34
Inter-individual variability (%)				
V_1	55.23	23.30	57.36	27.11–76.31
CL	15.78	76.70	16.00	4.27–33.50
Residual variability (%)	40.62	22.40	37.55	29.34–46.11

V_1, central volume of distribution; **V_2**, peripheral volume of distribution; **Q**, intercompartment clearance; **CL**, clearance; **RF**, renal function; **CW**, current weight in grams; **BW,** birth weight in grams; **PNA**, postnatal age in days; **RSE**, relative standard error.
In this population, 3220 g, 3100 g, and 8 days were the median current weight (day of the study), birth weight, and postnatal age values, respectively.

3.3. Covariate analysis

The allometric size approach was employed, which involved a priori inclusion of CW values into the basic model (allometric coefficient values of 0.75 for CL and Q and 1 for V_1 and V_2), which resulted in a significant decrease in OFV by 55.9 points. The most significant covariate on CL was postnatal age (PNA) (ΔOFV 10.4 points). Furthermore, birth weight (BW) and PNA together were demonstrated to be more significant than PNA alone (ΔOFV 25.0 points). No further decrease in the OFV was discovered by implementing other covariates. The medians (range) of the calculated weight-normalized CL and steady-state volume distribution (i.e. sum of V_1 and V_2) were 0.09 L/h/kg (0.05–0.14) and 0.95 L/kg (0.75–1.17), respectively. The steady-state $AUC_{0\text{-}24}$ of the evaluated dose regimen was between 438.17 mg*h/L and 1341.0 mg*h/L.

3.4. Model evaluation

3.4.1. Internal validation

In the final population PK model of latamoxef, acceptable goodness of fit was identified in model diagnostics. Unbiased predictions were observed in Figures 1A and 1B. No distinct patterns in the diagnostic plots of CWRES vs. time and PRED were observed (Figures 1C and 1D). Furthermore, the median parameter estimates generated from bootstrapping agreed with the respective values of the final population model. As shown in Table 1, a stable final model was obtained and population PK parameters could be estimated by re-determining with this model. The NPDE distribution and histogram agreed with the theoretical N (0, 1) distribution and density, thereby indicating that the model showed a good fit with the individual data (Figures 1E and 1F). The respective NPDE mean and variance were −0.0318 and 1.21, respectively.

3.4.2. External validation

Twenty patients from Beijing Children's Hospital and 19 patients from Beijing Obstetrics and Gynecology Hospital participated in the external validation. The median GA, PMA, and CW of patients in Beijing Children's Hospital were 38.5 weeks (range

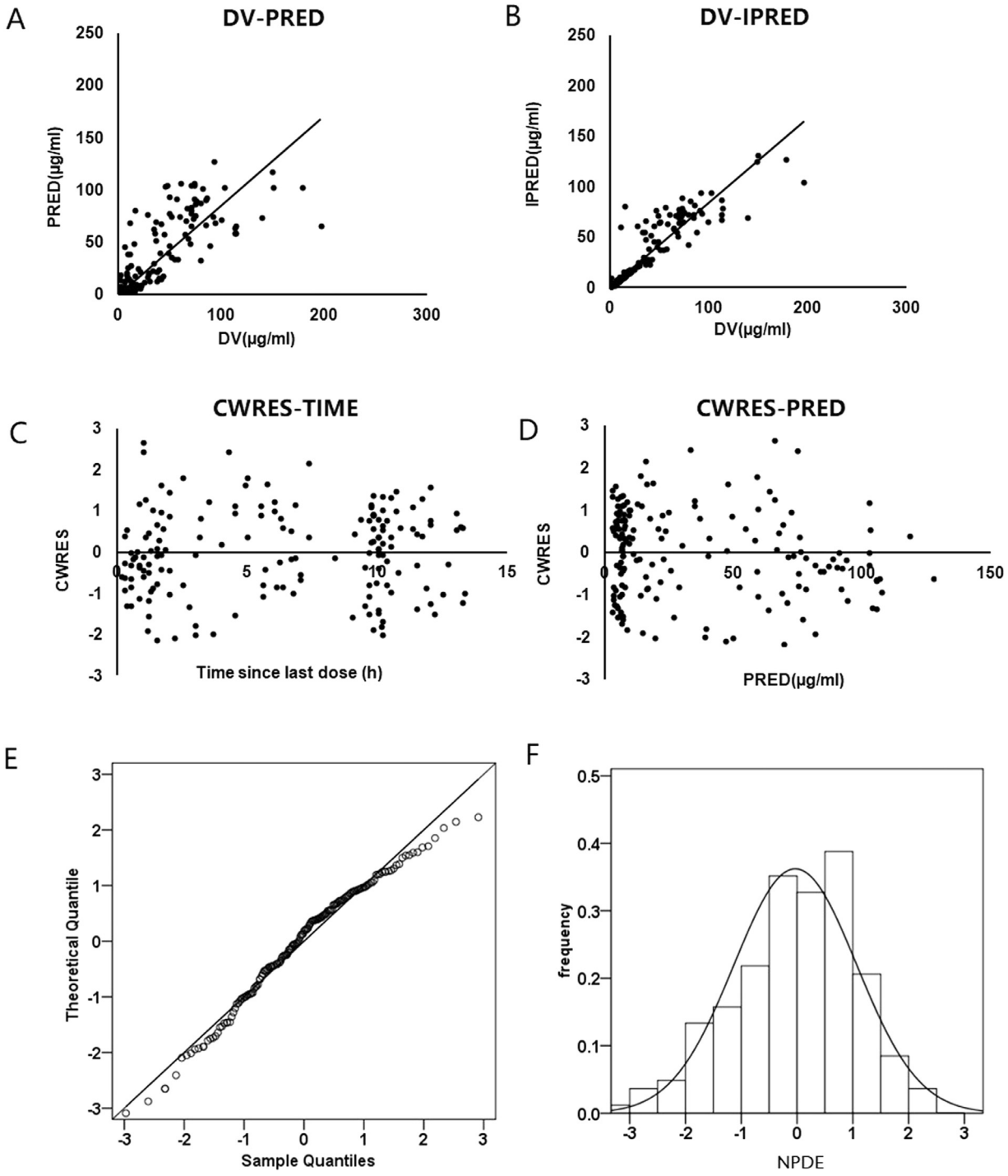

Figure 1. Model evaluation for latamoxef. A) Population predicted (PRED) vs. observed concentrations (DV); B) Individual predicted (IPRED) vs. observed concentrations (DV); C) Conditional weighted residuals (CWRES) vs. time; D): Conditional weighted residuals (CWRES) vs. Population predicted (PRED); E) QQ-plot of the distribution of the Normalized Prediction Distribution Errors (NPDE) vs. the theoretical N (0.1) distribution; F) Histogram of the distribution of the NPDE, with the density of the standard Gaussian distribution overlaid. The circles represent the prediction-corrected observed concentrations. The solid line represents the median prediction-corrected observed concentrations and semi-transparent grey field represents simulation-based 95% confidence intervals for the median. The observed 5% and 95% percentiles are presented with dashed lines and the 95% intervals for the model-predicted percentiles are shown as corresponding semi-transparent grey fields.

29.0–41.0), 39.3 weeks (range 32.0–42.0), and 3087.5 g (range 1460.0–4120.0), respectively. The mean (SD) MPE% and MAE% values of patients from Beijing Children's Hospital were 11.0 (24.4) and 19.3 (18.3), respectively. The percentage of these patients with MPE within ± 20% and MAE within ± 30% was 70.4% and 85.2%.

The median GA, PMA, and CW of patients from Beijing Obstetrics and Gynecology Hospital were 37.3 weeks (range 30.6–40.7), 39.9 weeks (range 31.0–43.7), and 3155.0 g (range 1480.0–3900.0), respectively. The mean (SD) MPE% and MAE% values of patients from Beijing Obstetrics and Gynecology Hospital were 1.6 (20.3)

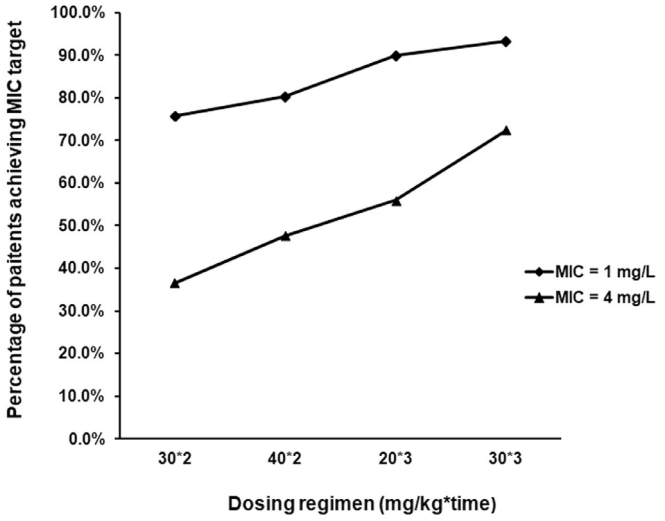

Figure 2. Dosing regimen optimization.

and 14.3 (14.1), respectively. The percentage of these patients with MPE within ± 20% and MAE within ± 30% was 70.0% and 85.0%.

3.5. Evaluation and optimization of the dosing regimen by Monte Carlo simulations

Target attainment as a function of the simulated doses for standard MIC susceptibility breakpoints, namely, 1 mg/L (*Escherichia coli* (*E. coli*), and *Klebsiella pneumoniae* (*K. pneumoniae*) to latamoxef) and 4 mg/L (*Stapphylococcus aureus* (*S. aureus*) to latamoxef), are presented in Figure 2. When the current dosing regimen (30 mg/kg q12h) was employed, 75.8% and 36.6% of neonates reached 70% $fT_{>MIC}$ with MICs of 1 mg/L and 4 mg/L, respectively. The application of this dosing regimen indicated that latamoxef was underdosing when the MIC was 4 mg/L. Using a shorter dosing interval of 8 h (30 mg/kg q8h), 72.4% of the neonates achieved 70% $fT_{>MIC}$ with MIC of 4 mg/L.

4. Discussion

This was the first large-scale investigation of latamoxef population PK in neonates and young infants (n = 128). It established an evidence-based dosing scheme for this population using developmental PK-PD.

The findings indicate a two-compartment model of the first-order elimination that is optimal for population PK data modelling. The median of the estimated steady-state weight-normalized CL was 0.09 L/h/kg (0.05–0.14). In the study by Schaad et al., the neonatal CL values varied from 0.06–0.11 L/h/kg and the CL value of infants aged < 1 year was 0.48 L/h/kg [11]. The CL values of newborns in the current study are similar to those in neonates and lower than those in infants, which were reported by Schaad et al. [11]. This discrepancy in CL values between neonates and infants may be attributed to renal maturation, as 99% of latamoxef is eliminated through glomerular filtration and active renal tubular secretion [12]. Renal anatomical and functional maturation that come with increasing age are expected to have a significant effect on CL of latamoxef. As the kidney is the main organ for elimination of latamoxef, different renal maturation surrogates were evaluated in covariate analysis. Because of the postnatal increase in glomerular filtration rate, it is thought that physiological factors (e.g. GA and PNA) exert a consistent effect on the PK of drugs, which are mostly eliminated by glomerular filtration. The CW, BW, and PNA were determined to be critical covariates for CL. The impact of BW and PNA on CL reflects the roles played by antenatal and postnatal renal maturation in the renal elimination of latamoxef.

Latamoxef is an oxacephem antibiotic that imparts time-dependent bactericidal effects [13]. This study found a correlation between PK-PD parameter of $fT_{>MIC}$ and therapeutic efficacy. The PK-PD target of 50% $fT_{>MIC}$ cephalosporins has been extensively characterized [14]. However, a goal of 70% $fT_{>MIC}$ is considered to be a more conservative endpoint in neonatal infectious diseases involving *E. coli, K. pneumoniae*, and *S. aureus*, as these are associated with both early-onset neonatal sepsis (EOS) and late-onset neonatal sepsis (LOS) [15,16]. Based on the bacterial susceptibility results of latamoxef in relation to these bacteria, the MIC values of *E. coli, K. pneumoniae*, and *S. aureus* are 0.12 mg/L, 1 mg/L, and 4 mg/L, respectively [17,18]. Simulation indicates that the current dosing regimen (30 mg/kg q12h) is adequate with MIC 1 mg/L. To reach the PK-PD target for more resistant bacterial species (e.g. *S. aureus*, MIC 4 mg/L), the current study adjusted the dosage or shortened the dosing interval (40 mg/kg q12h, 20 mg/kg q8h, and 30 mg/kg q8h). Monte Carlo simulation results suggest that shortening the dosing interval is most useful for improving > 70% $fT_{>MIC}$ attainment. An optimized dosing regimen using 30 mg/kg q8h was effective for treating *S. aureus* (MIC = 4 mg/L), as indicated by the higher PD parameter (72.4%). Because the latamoxef MIC values for treating *E. coli* were lower than those for *K. pneumoniae*, 30 mg/kg q12h can be utilized in treating infectious diseases due to *K. pneumoniae* and *E. coli*. In cases of more resistant bacterial species (e.g. *S. aureus*), a 30 mg/kg q8h regimen is required.

The current study had some limitations. Although serum creatinine concentration is an indicator of renal function, it did not show a significant influence on the CL of latamoxef. The narrow range values for creatinine in the samples may have caused this. In addition, because residual maternally derived creatinine could have an impact on neonate creatinine, this may not have been the best predictor of renal function in neonates [19]. Cystatin C (CysC), a recently discovered endogenous renal biomarker, has been shown to be a good biomarker of renal function in children with sepsis [20]. Thus, the potential role of CysC in drug clearance of newborns will need to be investigated in the future.

5. Conclusion

A population PK model for latamoxef was assessed using a large neonatal population. The CW, BW, and PNA showed significant effects on latamoxef PK. A model-based dosing regimen was designed to optimize latamoxef treatment of infectious diseases involving neonates and young infants. For latamoxef treatment of infectious diseases in newborns, dosing regimens of 30 mg/kg q12h or q8h were required for treating different pathogens.

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Competing Interests

None to declare.

Ethical Approval

This study was conducted in the Beijing Children's Hospital and the Beijing Obstetrics and Gynaecology Hospital. Ethics committee approval was gained from the ethics committee of each hospital (2017-k-45 and 2017-66). This study was also registered at ClinicalTrials.gov (NCT03113344).

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.11.017.

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