EP0943

Population pharmacokinetics, Monte Carlo simulations and dosing recommendations of cefepime using 90 minutes infusion, including renal impairment

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Introduction

Cefepime is a fourth cephalosporin with an extended antimicrobial spectrum against both Gram-positive and Gram-negative bacteria, including Amp-C producing Gram-negatives. Cefepime is being developed as a high -proportion combination with tazobactam as an extended infusion (WCK 4282), to extend its coverage against ESBL, Class C β-lactamases, and KPC producing micro-organisms.

Given the relatively poor availability of pharmacokinetic data and population models and the unavailability of data at high dosages of cefepime, pharmacokinetic studies were performed over up to one week of exposure. Data from volunteers, including those with renal impairment, receiving various dosing regimens were used to build a population pharmacokinetic model. Subsequently the results of the population model were used to perform Monte Carlo simulations (MCS). The effect of cefepime is known to be dependent on the %*f*T>MIC. Higher doses of cefepime and extended infusion may therefore provide coverage against micro-organisms with reduced susceptibility. We determined target attainment for various potential dosing schedules.

Materials and methods

Patients and dosing regimen

Between 2013 and 2016 pharmacokinetic studies were performed in healthy volunteers. Various dosing regimen of cefepime in combination with tazobactam were used. Cefepime and tazobactam were administered at a ratio of 1:1. In total of 90 subjects (65 males/25 females) received dosing regimens of 1gr or 2 gr cefepime (in combination with tazobactam) given either bid or tid with infusion times of 0.5-1.5 hour for up to 6-7 days. The renally impaired individuals received a single dose.

Blood sampling

Blood samples were collected just before the administration of the drugs and after infusion at 0.08, 0.5, 1, 1.5, 2, 4, 6.5 or 7 h, and trough during the whole first day and whole 6th day; peak and trough concentrations were determined on day 1-5. A total of 2951 concentrations were available for analysis. The renally impaired individuals were sampled up to maximally 30 hours after the start of the infusion.

Pharmacokinetic model

A population pharmacokinetic (PK) model was constructed using NONMEM (nonlinear mixed effects modelling, version 7.2, ICON Development Solutions, Ellicott City, MD, USA) with the IntelVisualFortran Compiler XE 14.0 (Santa Clara, CA, USA). To evaluate and visualise the different models RStudio (version 0.98.1028), R (version 3.1.1), Xpose (version 4.5.0) and PsN (version 4.2.0) were used in combination with the graphical interface Pirana (version 2.9.0). All data were analysed simultaneously.

Monte Carlo Simulation (MCS)

The estimates of the pharmacokinetic parameters and measures of dispersion were used to simulate various dosing regimens and obtain %*f*T>MIC ranges as a function of MIC. MCS was performed using the Miclab program, version 2.36 (Medimatics, Maastricht, NL) using 5000 cycles for each regimen. A protein binding of 20% was used. The output consisted of a probability distribution, a cumulative probability distribution, and specific confidence intervals over user defined MIC and %*f*T>MIC ranges.

Dosing regimen	Amount per dose	Rate of infusion	Dosing interval	Number of individuals
Multiple dose				
1	1000 mg	1000 mg/h	8h	18
2	1000 mg	2000 mg/h	12h	10
3	2000 mg	1333 mg/h	8h	8
4	2000 mg	1333 mg/h	12h	8
Single dose				
5	1000 mg	666.7 mg/h	n.a.	12
6	2000 mg	1333 mg/h	n.a.	34

Table 2. Different dosing regimen and number of patients per group. n.a.: not applicable.

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	Mean	Range
Age (y)	45.4	18 - 77
Weight (kg)	75.3	52.5 - 113.8
BMI (kg/m2)	25.2	18.9 - 37.5
Creatinine clearance (ml/min)	103.2	7.9 - 191.7
Serum creatinine (µmol/L)	37.6	0.5 - 97
Sex (male/female)	65/25	

Table 1. Characteristics of the study-population of 90 healthy volunteers

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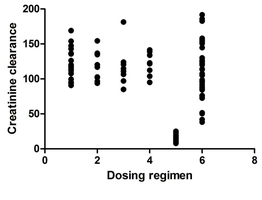

Figure 1. Distribution of the different dosing regimen (table 32 over the values for the creatinine clearance.

3 6

	Run 155 final (3 covariates)			Run147 (only CrCL on CL)		
Parameter	Mean	SE	Relative SE (%SE)	Mean	SE	Rel. SE (%SE)
Θ1: Clearance (liters/h)[a]	5.2	0.080	1.5	5.2	0.080	1.5
Θ2: V1 (liters) [a]	8.1	0.53	6.5	8.1	0.53	6.5
Θ3: V2 (liters)	7.5	0.38	5.1	7.7	0.48	6.2
Θ4: Intercompartmental clearance V1 and V2 (L/h)	10.7	1.26	11.8	10.8	1.27	11.8
Θ5: additive error	1.3	0.28	22.3	1.3	0.28	22.1
Θ6: proportional error	0.097	0.0059	6.1	0.097	0.0059	6.1
Θ7: Covariate creatinine-CL on CL	0.87	0.028	3.2	0.87	0.028	3.2
Θ8: Covariate creatinine clearance on V2	-0.19	0.039	20.6	-	-	-
Θ9: covariate weight on V2	0.74	0.18	24.3	-	-	-
η1: Variability on clearance [Shrinkage 1.7/ 1.6%]	0.023	0.0043	18.4	0.23	0.0042	18.3
η2: Variability on V1 [Shrinkage 3.6/3.7%]	0.087	0.038	43.4	0.091	0.039	42.9
η3: Variability on V2 [Shrinkage 10.7/7.1%]	0.049	0.011	22.4	0.085	0.02	23.6

Table 2. Estimates of the final population PK model (155) consisting of 2 compartments, variability on CL, V1 and V2, and covariates creatinine clearance on the clearance of cefepime, creatinine clearance on V2 and weight on V2. The second model presented is the model only including creatinine clearance as covariate on the cefepime clearance.

Summary of Results

1 **90 healthy volunteers were included in the PK-analysis (table 1).**

2 **The different dosing regimens are shown in table 2.**

The different creatinine clearance per dosing regimen are shown in figure 1.

3 **A two compartment model best described the PK-data including (run 155):**

1 **Creatinine clearance as covariate on clearance.**

2 **Creatinine clearance as covariate on V2.**

3 **Weight as covariate on V2.**

4 **Correlation between the covariates and the PK-parameters estimates (figure 2).**

5 **Diagnostic plots illustrate that the model fits the data well (figure 3)**

6 **To perform MCS the model with only creatinine clearance as covariate on CL was used (run147).**

7 **MCS: By using the currently proposed dosing regimen of 2 gram cefepime TID infused over 90 minutes and a target MIC of 16 mg/L, the values for the %*f*T>MIC for the lower 99% and 95% percentile, were 51.9% and 57.8%, respectively.**

8 **MCS: In patients/subjects with various degrees of renal impairment, the MIC of cefepime was determined for a PTA >90% and >97.5% for a target of 50% *f*T>MIC (table 4) for various dosing regimens.**

Suggested dose adjustments are 1000mg tid for clearance of 30-60 mL/min, 500mg tid for 15-29 mL/min, 250mg tid for 10-15 mL/min.

9 **For patients/subjects with a high clearance (120-180 mL/min) extended infusion to 4h of the 2gr cefepime dose provided overage with a >99% target attainment for a target of 50% *f*T>MIC at an MIC of 16 mg/L.**

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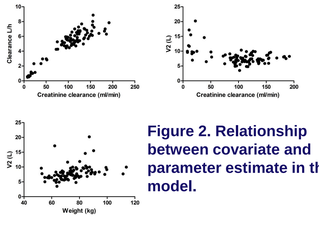

Figure 2. Relationship between covariate and parameter estimate in the model.

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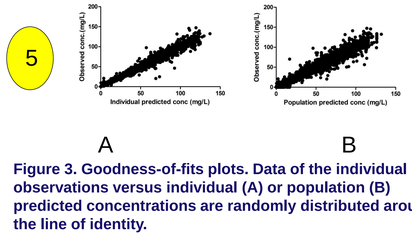

A B

Figure 3. Goodness-of-fits plots. Data of the individual observations versus individual (A) or population (B) predicted concentrations are randomly distributed around the line of identity.

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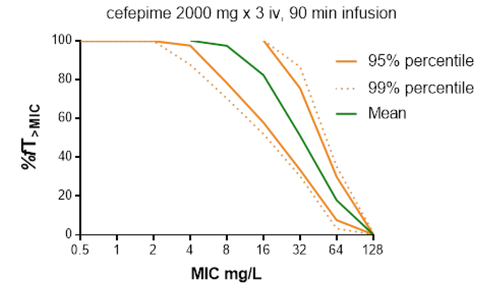

Figure 4. Monte Carlo Simulations using the Population PK model of cefepime including the covariate CrCL on CL. A normal renal function was used in the simulations.

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Dose	Standard	60 mL/min	50 mL/min	30 mL/min	15 mL/min	10 mL/min
2000 mg x 3	16/16	32/32	32/32	-	-	-
1000 mg x 3	-	16/16	16/16	32/32	-	-
500 mg x 3	-	8/8	8/8	16/16	32/32	-
250 mg x 3	-	-	-	8/8	16/16	16/16
500 mg x 2	-	-	-	-	8/8	32/32
250 mg x 2	-	-	-	-	-	16/16
250 mg x 1	-	-	-	-	-	8/8

Table 4. Minimum MICs (mg/L) of cefepime for a PTA > 90% and > 97.5% (presented as x/x, respectively) for various clearance values at the 50% fT>MIC target and a duration of infusion of 90 minutes. Column headings indicate clearance .

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MIC	120 mL/min	150 mL/min	180 mL/min
8 mg/L	>99.9	>99.9	>99.9
16 mg/L	>99.9	>99.9	99.4

Table 5: PTA of cefepime given as 2 g by 4 h infusion using a target of 50% %*f*T>MIC in subjects with increased renal clearance.

Conclusions

- **The pharmacokinetic data were best described by a two-compartment model.**
- **Covariates were creatinine clearance on clearance and the peripheral volume of distribution (V2) and weight on V2.**
- **MCS indicates that the currently proposed dosing regimen of 2 gram cefepime every 8 hours infused over 90 minutes results in a probability of target attainment of 99.8% taking into account a 50% %*f*T>MIC target and an MIC of 16 mg/L.**
- **Dosing regimens for the renally impaired are suggested. For patients with a high renal clearance (120-180 ml/min) adequate PTA can be reached by increasing the infusion duration to 4 hours.**