Cerebrospinal fluid pharmacokinetics of ceftaroline in neurosurgical patients with external ventricular drain

Pascal Chavanet, Alexia Chauzy, Nadine Defrance, Abdelouaïd Nadji, Jean-Christophe Combes, William Couet, Lionel Piroth

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Chavanet P [1]; Chauzy A [2]; Defrance N [3]; Nadji A [3]; Combes JC [3]; Couet W [2]; Piroth L [1]

[1] Département d'Infectiologie, CHU and INSERM CIC1432, Université de Bourgogne, Dijon, France ; [2] Université de Poitiers, INSERM U1070, CHU Poitiers, Poitiers, France; [3] Neuroréanimation, Hôpital du Bocage, CHU Dijon, Dijon, France

INTRODUCTION

- Ceftaroline is a broad spectrum cephalosporin with activity against drug-resistant bacteria, including strains of methicillin-resistant *Staphylococcus aureus* (MRSA) [1,2], and could be attractive for prevention or treatment of bacterial post-neurosurgical meningitis. However, only few data are available concerning its meningeal concentrations [3].
- The aim of this study was to assess the distribution of ceftaroline into the cerebrospinal fluid (CSF) in intensive care unit (ICU) patients with an external ventricular drain (EVD) at risk or with suspicion of meningitis.

METHODS

Ethics

- This study was approved by the local ethics committee (Comité de Protection des Personnes Est-I, # 2014-004138-25) and authorised as a clinical study by the national drugs administration (Agence Nationale de Sécurité du Médicament).

Study design

- Nine patients with suspected post neurosurgical meningitis and hospitalized in the neurosurgery intensive care unit of Dijon University Hospital were included in the analysis.
- Patients received a single 600 mg dose of ceftaroline as a one-hour intravenous infusion.
- Plasma and CSF samples were collected before and 0.5, 1, 3, 6, 12 and 24 hours after the end of the infusion. CSF sampling was performed via the EVD system.
- All samples were assayed at Covance laboratory by LC-MS/MS.

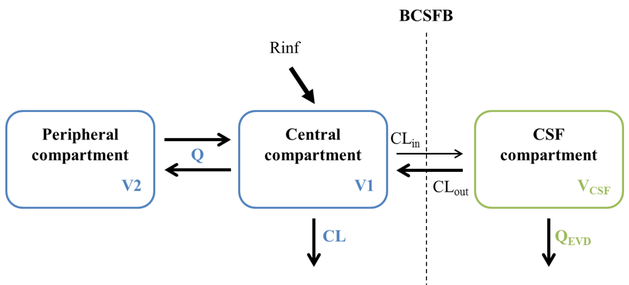

Figure 1. Schematic representation of ceftaroline final PK model used to describe total plasma and unbound CSF concentrations.

Population pharmacokinetic analysis

- Ceftaroline concentrations in plasma and CSF were analyzed using the nonlinear mixed effects modeling approach in NONMEM software version 7.4.
- A two-steps compartmental PK analysis was conducted:
  1) ceftaroline plasma data were first analyzed,
  2) plasma parameters estimated and corrected for protein binding of 20% [2] were fixed to fit unbound CSF concentrations.
- The influence of various patient characteristics on the parameter estimates were investigated.

RESULTS

- Observed peak concentrations in CSF (0.22 ± 0.17 µg/mL) were much lower than plasma peak concentrations (18.29 ± 3.33 µg/mL) and EUCAST clinical MIC breakpoint for susceptibility to ceftaroline among *S. aureus* isolates (2 µg/mL) [4] (**Figure 2**).
- Total plasma concentrations of ceftaroline versus time were best fitted by a two-compartment model with first-order elimination. After the inclusion of CSF data, the model was expanded and a three-compartment model was used to describe all ceftaroline concentrations simultaneously (**Figure 1**).
- Elimination of ceftaroline from the CSF via the EVD was taken into account by fixing the flow rate of the EVD (QEVD) for each patient to its experimental value.

Table 1. Typical estimates for ceftaroline pharmacokinetic parameters

Parameter	Estimate (RSE%)	IIV CV% (RSE%)
$CL = CL_{pop}*EXP[CLcr_{cov}*(CLcr-6.9)]$		
CL_{pop} (L/h)	11.3 (5)	15.9 (44)
$CLcr_{cov}$	0.0047 (23)	
$V1 = V1_{pop}*(BW/79)$		
$V1_{pop}$ (L)	28.4 (10)	16.6 (102)
Q (L/h)	6.06 (20)	
V2 (L)	11.0 (12)	
$CLin = CLin_{pop}*[(GLY/3.9)^{**}GLY_{cov}]$		
$Clin_{pop}$ (mL/h)	1.39 (17)	54.0 (50) [a]
GLY_{cov}	-3.0 (10)	
CLout (mL/h)	14.8 (18)	54.0 (50) [a]
V_{CSF} (L)	0.15 [b]	

CLcr, creatinine clearance (L/h); BW, body weight (Kg); GLY, glycorrhachia (mmol/L).
[a] A same IIV was estimated for CLin and CLout.
[b] V_{CSF} was fixed to a value corresponding to the physiological volume of CSF [5].

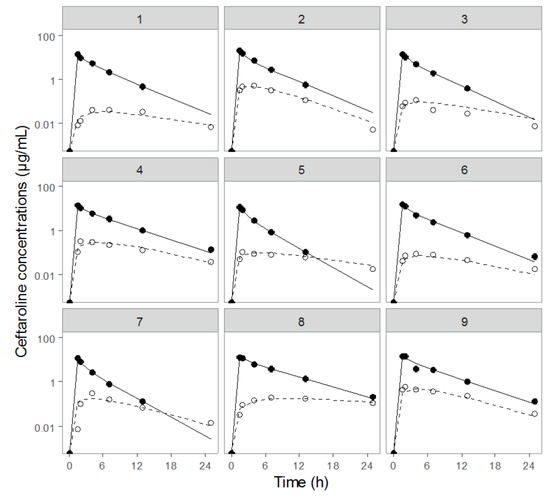

Figure 2. Total plasma and unbound CSF concentration-versus-time profiles for ceftaroline. Circles correspond to observed concentrations in plasma (●) and in CSF (○). Solid and dashed lines represent, respectively, individual concentrations predicted by the PK model in plasma and in CSF.

- The bidirectional passage across the blood cerebrospinal fluid barrier (BCSFB) was characterized by a clearance into the CSF (CLin) and a clearance out of the CSF (CLout) (**Figure 1**). Estimated CLin was much lower than CLout (**Table 1**) with a corresponding typical CLin/CLout ratio, which characterizes ceftaroline distribution within the CSF, equal to 9.4%.
- A negative correlation between glycorrhachia and CLin was identified indicating that the diffusion of ceftaroline into the CSF was inversely related to the CSF glucose levels (**Table 1, Figure 3**). Mean glycorrhachia of 4.39 mmol/L suggested that patients of the present study presented only a slight inflammation of their meninges.

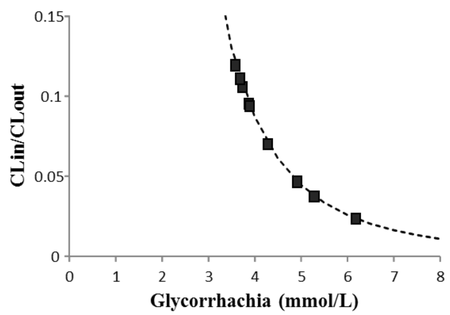

Figure 3. Correlation between ceftaroline penetration factor into CSF (CLin/CLout ratio) and glycorrhachia. Squares correspond to observed CLin/CLout ratio and dashed line represents mean CLin/CLout ratio predicted by the model .

CONCLUSIONS

- **Following a single infusion of 600 mg, ceftaroline penetration into the meninges is limited, with a CSF exposure equal to only 9.4 % of systemic exposure on average. CSF concentrations are then too low for ensuring prophylactic protection or therapeutic effect against most pathogens with MICs between 1 and 2 mg/L.**
- **However, the model suggests that in case of meningitis with a low glycorrhachia (< 1.9 mmol/L) [5], ceftaroline CSF exposure would be much greater.**
- **Additional studies aiming at assessing the distribution following multiple higher doses are needed.**

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