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# Pharmacokinetics of Cefepime-Enmetazobactam in the Cerebrospinal Fluid of Rats

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## Introduction

**Nosocomial meningitis** caused by Gram-negative pathogens remains a major therapeutic challenge, particularly with the increasing prevalence of multidrug-resistant bacteria that restrict available treatment options. **Cefepime** is standard care, but its activity is increasingly compromised by β-lactamase–mediated resistance [1]. **Enmetazobactam**, a novel extended-spectrum β-lactamase inhibitor, has been developed to restore the antibacterial spectrum of cefepime. To evaluate the potential applicability of this combination for **central nervous system (CNS) infections**, we investigated the **pharmacokinetics of cefepime/enmetazobactam in cerebrospinal fluid (CSF) of rats**.

## Materials and methods

- Experiments were conducted in accordance with EC Directive 2010/63/EU after approval by the local ethics committee (authorization number: 55247-2025042216508773).
- Thirty-eight healthy Sprague-Dawley rats weighing 308 ± 67 g were used.
- Cefepime/enmetazobactam was administered as an intravenous bolus via the tail vein at a dose of 50/25 mg/kg in anesthetized rats.
- Blood and CSF samples were collected over 210 min in a minimum of 3 animals per sampling time. Blood samples were collected by intracardiac puncture while CSF was collected from the cisterna magma. Plasma was separated from whole blood after centrifugation at 11000 g for 10 min at 4°C.
- Cefepime/enmetazobactam concentrations in plasma and CSF were determined by LC-MS/MS. The plasma protein binding of both compounds was found to be negligible in prior investigations and was consequently assumed to be zero [2].
- A sparse non-compartmental pharmacokinetic analysis was conducted using PKNCA R package [3].

## Results

- Mean PK parameters are presented in Table 1.
- Compared with plasma, CSF concentration-time profiles were flat for both compounds (Figure 1), reflecting slow and limited distribution, with CSF-to-plasma AUC ratios of 4.93% and 4.86% for cefepime and enmetazobactam, respectively.

**Table 1.** Mean pharmacokinetic parameters obtained by sparse noncompartmental analysis in healthy rats after intravenous bolus administration of 50/25 mg/kg of cefepime (FEP)/enmetazobactam (META).

| Matrix | Parameter | Unit | FEP | META |
|---|---|---|---|---|
| Plasma | C0 | mg/L | 284 | 314 |
| | $t_{1/2}$ | min | 25.2 | 22.3 |
| | $AUC_{0-\infty}$ | h*mg/L | 109 | 85 |
| | CL | L/(h*kg) | 0.460 | 0.294 |
| | Vd | L/kg | 0.279 | 0.157 |
| CSF | Cmax | mg/L | 1.59 | 1.57 |
| | Tmax | min | 60 | 20 |
| | $t_{1/2}$ | min | 108 | 85.3 |
| | $AUC_{0-\infty}$ | h*mg/L | 5.36 | 4.16 |

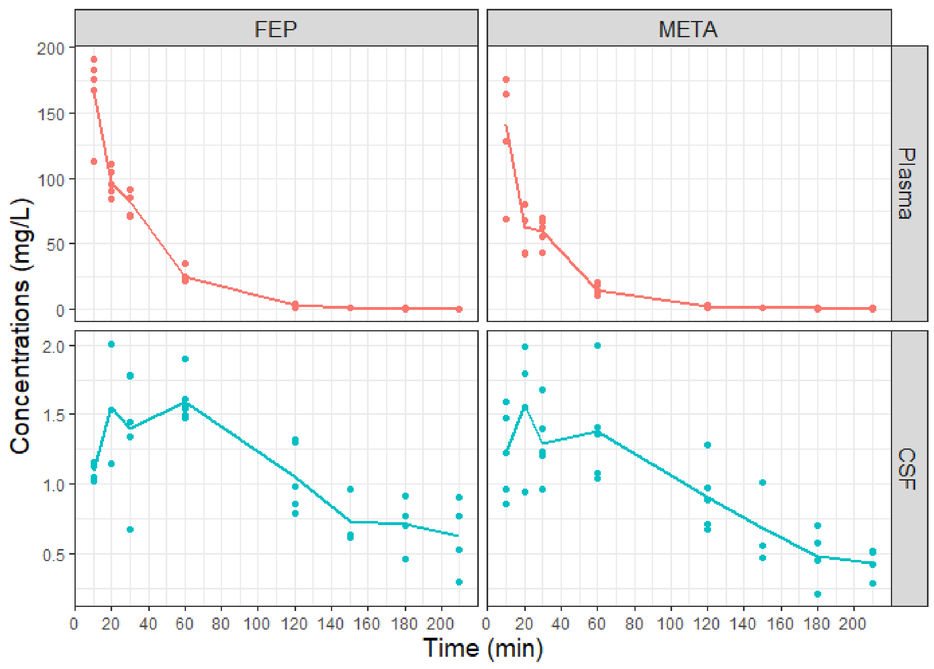


**Figure 1:** Plasma and CSF concentrations of cefepime (FEP) and enmetazobactam (META) in rats (n=3-5 per time point).

## Conclusion

Although both compounds showed **limited CSF penetration**, the cefepime AUC ratio was consistent with the range of previously reported values [4]. Importantly, these results provide **the first available CSF penetration data for enmetazobactam**. Overall, our findings provide initial pharmacokinetic data to **further investigate the potential role of cefepime/enmetazobactam in CNS infections.**

**References:**

[1] Gorham et al. 10.1080/14787210.2025.2565581

[2] Crandon et al. 10.1128/AAC.00033-15

[3] Denney et al. 10.1007/s10928-015-9432-2

[4] Lodise et al. 10.1016/j.diagmicrobio.2005.09.007

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