Epithelial lining fluid penetration of temocillin administered by continuous infusion in critically ill patients with nosocomial pneumonia.

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Background

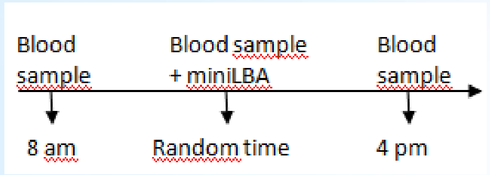
- Temocillin is a β-lactam increasingly used in serious infections caused by Enterobacteriaceae, including ESBLs and even some carbapenemase-producing strains, as an alternative to carbapenems, especially in critically ill patients (1-5) .
- Temocillin is licensed in UK, France, and Belgium for lower respiratory tract infections although clinical data are scarce and no data about Epithelial Lining Fluid (ELF) concentrations are available.

Objective

We aim to determine serum and ELF temocillin concentrations administered by continuous infusion (CI) in critically ill patients with nosocomial pneumonia.

Material/methods

- 10 adult patients with severe bacteriologically documented nosocomial pneumonia occuring in ICU were prospectively enrolled and received CI of 6g/day of temocillin after a 30-min 2g loading dose.
- Plasma and ELF samples were obtained at steady-state and total and free concentrations of temocillin were measured by UHPLC-MS/MS method. Concerning the determination of free temocillin concentrations, an ultracentrifugation prior to UHPLC-MS/MS method was performed (6) .
- Timing of serial plasma and unique ELF samplings (n = 10) per patient was as follow:



Results

- Samplings were performed at mean (± SD) 33.2 ± 22.8 hours after the start of CI.
- The mean (± SD) creatinine clearance based on 24h urine was 112.2 ± 40.7 ml/min/1.73m^2, including 3 patients with value > 120 ml/min/1.73 m^2 and 1 patient receiving CVVH.
- Total and free temocillin concentrations and AUC in both plasma and ELF and their respective ELF/plasma ratios are presented in Table 1.
- A high pharmacokinetic interindividual variability was observed in plasma and ELF for both total and free concentrations but these concentrations remained stable intraindividualy in plasma such as illustrated in Figure 1.

Table 1.

		Plasma (mean ± SE)	ELF (mean ± SE)	ELF/plasma ratio (mean ± SE)
Total temocillin concentration (mg/L)		68.0 ± 11.3	9.8 ± 1.3	0.17 ± 0.03
Free temocillin concentration (mg/L)		17.3 ± 4.8	9.8 ± 1.6	0.84 ± 0.18
		Plasma	**ELF**	**ELF/plasma ratio**
AUC_{0-24} (mg.h/L)	**Total temocillin**	1632	235	0.14
	Free temocillin	415	235	0.57

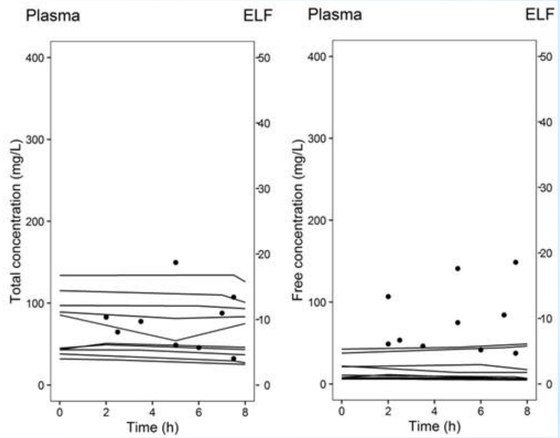


Figure 1.
(●) ELF concentrations: one sample per patient
(—) Plasma concentrations: three samples per patient

Conclusions

The administration of 6g per day of temocillin by continuous infusion in critically patients with severe nosocomial pneumonia allows a penetration ratio, measured by the ELF/plasma ratio of AUCs, of 0.14 and 0.57 and a mean (± SE) ELF concentration , in mg/L, of 9.8 ± 1.3 and 9.8 ± 1.6 for total and free drug, respectively. Standard error of AUCs should be calculated by the Bootstrap method and Monte Carlo simulations should be performed for subsequent PK/PD analysis.

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