Matznneller *et al.: Intrinsic Activity*, 2018; **6**(Suppl.1):A5.2
doi:10.25006/IA.6.S1-A5.2
published online: 20 September 2018

24th Scientific Symposium of the Austrian Pharmacological Society

Graz, 27–28 September 2018

MEETING ABSTRACT

A5.2

Soft-tissue pharmacokinetics of ceftolozane/tazobactam: room for dose optimization?

Peter MATZNELLER[1], Valentin AL JALALI[1], Edith LACKNER[1], Christoph DORN[2], Alexander KRATZER[3], Beatrix WULKERSDORFER[1], Zoe ÖSTERREICHER[1] and Markus ZEITLINGER[1,*]

[1]Department of Clinical Pharmacology, Medical University of Vienna, Austria; [2]Department of Clinical Pharmacy, University of Regensburg, Germany; [3]Hospital Pharmacy, University Hospital Regensburg, Germany

Background: Ceftolozane/tazobactam (CEF/TAZ) is a novel antibiotic to treat multi-resistant Gram-negative infections including soft-tissue infections. Available information of pharmacokinetics (PK) of CEF/TAZ in soft tissue and plasma protein binding is fragmentary.
Methods: We investigated single and repeated dose PK of CEF/TAZ in plasma, muscle and subcutis of eight healthy volunteers receiving 1.5 g CEF/TAZ as 1 h intravenous infusion every 8 hours. CEF/TAZ concentrations in muscle and subcutis were measured by micro-dialysis. Plasma protein binding was determined by ultrafiltration.
Results: Single and repeated dose concentration-time profiles of CEF/TAZ in investigated compartments are shown in Fig. 1. Mean plasma protein binding was 6.3% and 8.0% for CEF and TAZ, respectively. Taking plasma protein binding into account, unbound tissue/plasma AUC_{last} ratios after repeated dose were approximately 0.9 for both muscle and subcutis. Between single and repeated dose no appreciable accumulation occurred in plasma and subcutis. However, both CEF and TAZ showed pronounced accumulation in muscle after repeated dose, with an increase in mean AUC_{last} of 33% and 23% compared to single dose, respectively. Using the Entero-bacteriaceae breakpoint of 1 mg/l, time above minimal inhibitory concentration (MIC) for unbound plasma CEF ($fT > MIC$) after repeated dose was 100%. For TAZ, the currently discussed PK/PD index time above a threshold concentration ($T > C_T$, where C_T is calculated as 0.5 × MIC of ceftolozane) was 52.2%, which is markedly below the value of 75.7% associated with 1-log killing according to literature [1].
Discussion: Plasma exposure of CEF/TAZ in the present study was lower compared to previous data in healthy volunteers. In terms of soft-tissue PK, this study amends existing data showing marked accumulation in muscle. After repeated doses, concentrations were comparable between subcutis and muscle. Remarkably, plasma protein binding of CEF and TAZ was considerably lower than previously reported. Review of the current literature on relevant PK/PD targets for CEF/TAZ suggests sufficient exposure for CEF but possibly subtherapeutic levels for TAZ at the evaluated dosing regimen.

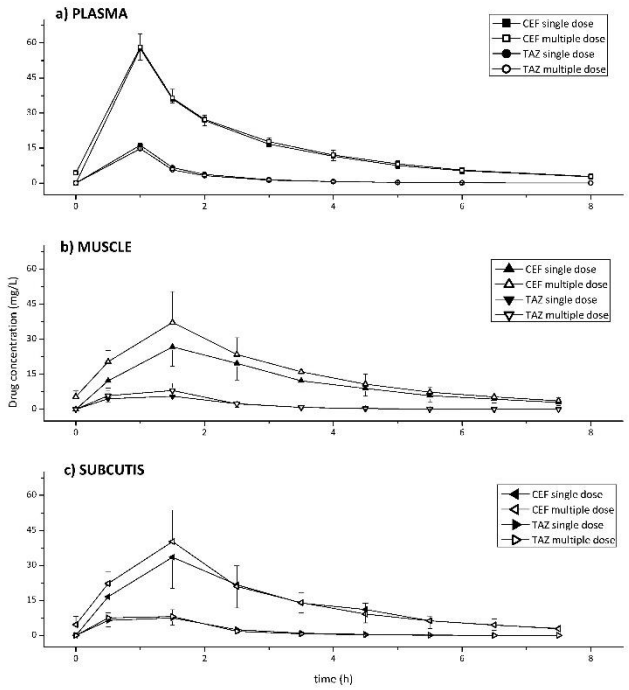

Figure 1: Concentration–time profiles of ceftolozane (CEF) and tazobactam (TAZ) in (**a**) plasma, (**b**) muscle and (**c**) subcutis in healthy volunteers following single or multiple intravenous doses of 1.5 g CEF/TAZ (means ± standard deviation, $n = 8$).

Reference

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*Corresponding author e-mail: *markus.zeitlinger@meduniwien.ac.at*