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Objectives:

Methods:

Results:

Conclusion:

References:

[1] A.B. Author. J. Antimicrob. Chemother. 76: 12-18 (2013)

[2] W.X.Y. Writer. In: C. Cordovil et al. (eds.) Proceedings of the Workshop xxx. Lisbon/Portugal, 270-271 (2014)

[3] A.B. Author (eds): Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, Springer, Stuttgart/Germany, 2nd edition (2014)

Example

Characterisation of plasma and target-site cefazolin pharmacokinetics and
protein binding in obese and nonobese patients

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Objectives: Cefazolin (CEZ) is frequently used for the treatment of skin and soft tissue infections (SSTI), e.g. after surgery. Obesity has been identified as a risk factor for surgical site infections, but data for a quantitative evaluation of its pharmacokinetics (PK) in the interstitial space fluid (ISF) of subcutaneous (s.c.) adipose tissue (i.e. the target site for the treatment of SSTI) in obese patients are scarce. The aims of this model-based analysis were to quantify (i) CEZ protein binding kinetics and (ii) target-site penetration in obese *versus* nonobese surgical patients.

Methods: Previously published data [1,2] from 15 obese (BMImedian=52.6 kg/m2) and 15 nonobese patients (BMImedian=26.0 kg/m2), receiving a single dose of 2000 mg CEZ (30-min intravenously) for infection prophylaxis before abdominal surgery, were included in the analysis [1,3]. Rich PK sampling was available over 8 h in plasma (ntotal=240) and via microdialysis in the ISF of s.c. adipose tissue (ntotal=591). Plasma samples were additionally subjected to ultrafiltration to measure unbound CEZ concentration (ntotal=120). Nonlinear mixed-effects (NLME) PK modelling was applied to characterise CEZ protein binding kinetics and to evaluate differences in target-site penetration index, as the ratio of unbound CEZ AUC0-8h in target-site:plasma (PI=*f*AUCtarget, 0‑8h/*f*AUCpla, 0-8h), between patient groups.

Results: Preliminary results by a two-compartment (target-site concentrations attributed to the peripheral compartment) NLME PK model with interindividual variability on clearance and the central volume of distribution suggested that CEZ exhibits saturable protein binding, with a maximum binding capacity (Bmax) of 234 mg/L and dissociation constant (Kd) of 60.6 mg/L. Precision of the parameter estimates was high (relative standard error≤27.9%) and PI appeared lower in obese (PImedian=0.576, range=0.464-0.717) *versus* nonobese patients (PImedian=0.651, range=0.516-0.850).

**Conclusion:** The preliminary results were in line with previous studies that suggested saturable binding of CEZ [1,4]. Potential differences in PI between obese and nonobese patients and their clinical relevance will be investigated in the future.

References:

[1] C. Dorn et al. J. Antimicrob. Chemother. 76: 2114–2120 (2013)

[2] C. Dorn et al. J. Chromatogr. B, 1118–1119: 51-54 (2019)

[3] P. Simon et al. Contemp. Clin. Trials Commun. 15: 100375 (2019)

[4] M.J.E. Brill et al. J. Antimicrob. Chemother. 69: 715–723 (2014)