Cefepime/enmetazobactam steady-state concentrations in spondylodiscitis-relevant tissues – an experimental porcine study

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Introduction

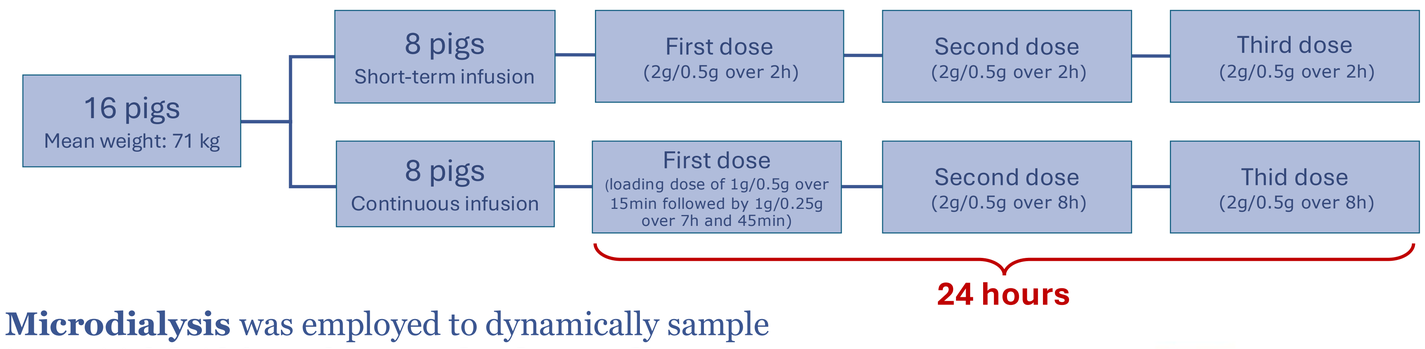
Spondylodiscitis is a severe infection with substantial morbidity and mortality.

Gram-negative organisms account for approximately **25–30%** of cases and can be challenging to treat.

Cefepime/enmetazobactam is a novel cephalosporin/β-lactamase inhibitor combination with activity against ESBL-producing Gram-negative pathogens

Methods

Sixteen pigs were randomised to receive either short term infusion of cefepime/enmetazobactam or continuous infusion in three dosing intervals of 8 hours.



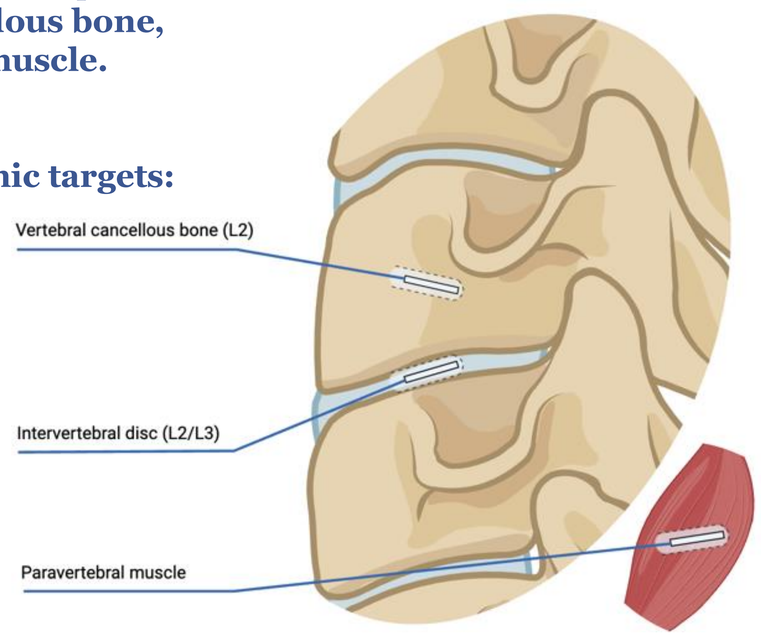
Microdialysis was employed to dynamically sample interstitial fluid from the **Vertebral cancellous bone, Intervertebral disc** and **paravertebral muscle.** Plasma samples were collected as reference.

Key pharmacokinetic/pharmacodynamic targets:

For cefepime T>MIC:
Enterobacterales: 4 ug/mL
Pseudomonas Aeruginosa: 8 mg/mL

For enmetazobactam T>C_t
2 ug/mL

And aggressive targets of 4xMIC and 4xC_t



Results

For cefepime: At the conventional MIC targets 4 and 8 mg/L, all compartments achieved 100% T>MIC during the third dosing interval, regardless of administration. At the aggressive target of 32 mg/L, continuous infusion resulted in longer T>MIC than short-term infusion in vertebral cancellous bone and intervertebral disc.

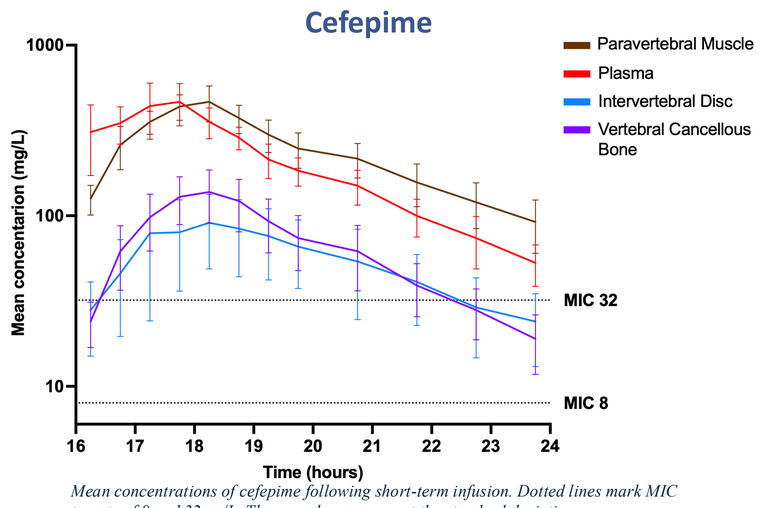
For enmetazobactam: At the conventional Cthreshold of 2 mg/L, all compartments achieved 100% T>Cthreshold, regardless of administration. At the aggressive Cthreshold of 8 mg/L, continuous infusion resulted in longer T>Cthreshold than short-term infusion in vertebral cancellous bone and intervertebral disc

Conclusions

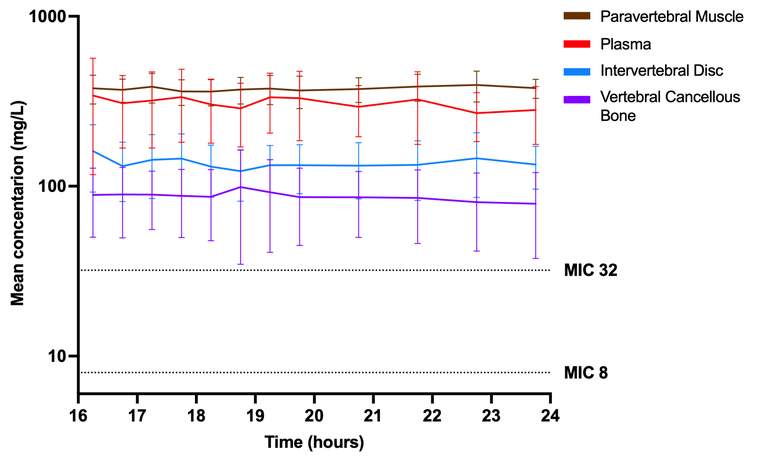
Cefepime/enmetazobactam consistently reached theoretically effective unbound steady-state tissue levels in vertebral bone, intervertebral disc and paravertebral muscle, regardless of the mode of administration

Continuous infusion provided an advantage only at the most aggressive targets (cefepime 32 mg/L; enmetazobactam 8 mg/L).

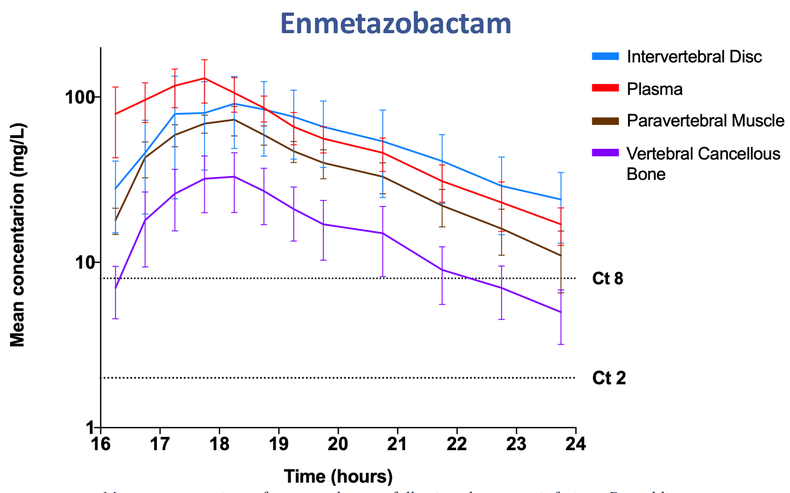
Concentration-time profiles



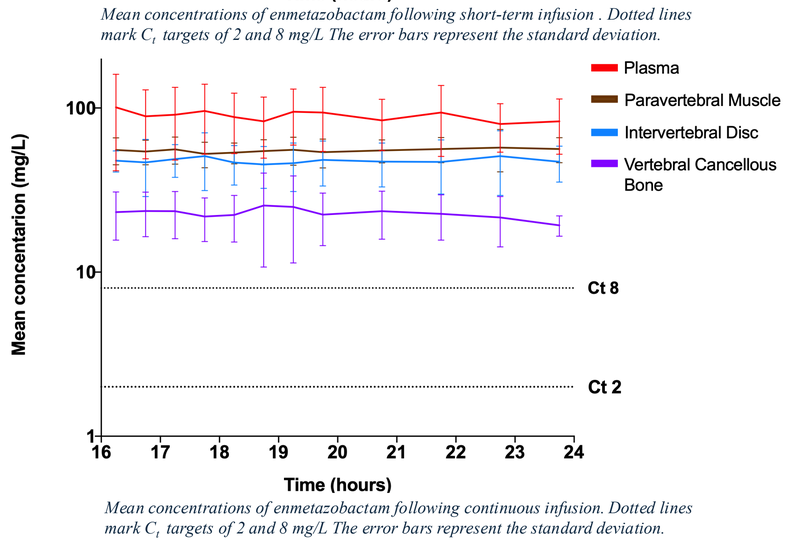
Mean concentrations of cefepime following short-term infusion. Dotted lines mark MIC targets of 8 and 32mg/L. The error bars represent the standard deviation



Mean concentrations of cefepime following continuous infusion. Dotted lines mark MIC targets of 8 and 32 mg/L. The error bars represent the standard deviation



Mean concentrations of enmetazobactam following short-term infusion . Dotted lines mark C_t targets of 2 and 8 mg/L The error bars represent the standard deviation.



Mean concentrations of enmetazobactam following continuous infusion. Dotted lines mark C_t targets of 2 and 8 mg/L The error bars represent the standard deviation.

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