A1-026

IN VIVO PK/PD OF MECILLINAM IN A MURINE URINARY TRACT INFECTION (UTI) MODEL

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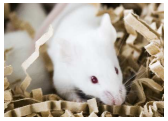
BACKGROUND

Mecillinam, MEC, (amdinocillin) is a promising drug for treatment of urinary tract infection (UTI) caused by ESBL-producing E.coli. We used an UTI model in mice to identify the PK/PD index that best correlates with efficacy of MEC.

MATERIALS AND METHODS



PK- Studies

The PK characteristics of MEC was studied in OF-1 mice after single SC doses of 0.26 to 66.7 mg/kg. Blood and urine was collected from mice (n=3) starting at 6 min to 2 hrs after dosing and the drug levels were determined by MS.

Efficacy Studies

Urinary tract infection was induced via urethral catheterization with an ESBL-producing (CTX-M9) E.coli. Mice (n=8) were treated once, twice or four times daily at day 1 and 2 post infection. Urine, bladders and kidneys were collected day 3 post infection for CFU determination. Each dot in the figures above represents the mean of 8 mice.

PKPD modeling

Estimation of T>MIC, AUC_{24} and C_{max} for the various dosage regimens was done with the PKPDsim software package (1) based on the concentration-time points from the five primary single-bolus PK-studies.

References

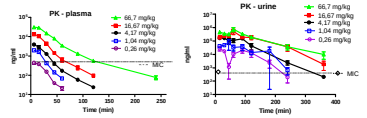
1) PKPDsim software homepage, http://www.ssi.dk/pkpdsim

CONCLUSION

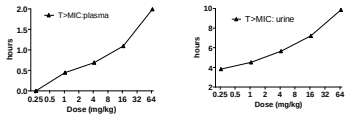
The murine experimental UTI model provides a means of studying PK/PD at clinically relevant sites of infection. Here we show that for MEC, the PD parameter that best correlated with efficacy was %T>MIC, and that very low values in blood, < 5% correlated with values of 33–46% in the urine.

Dose dependent Pharmacokinetics

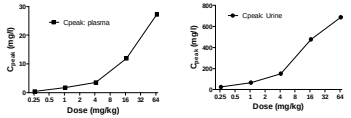
Plasma and urine concentration of MEC after single dosing



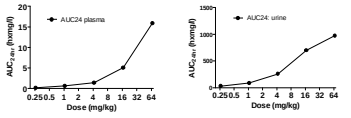
T>MIC



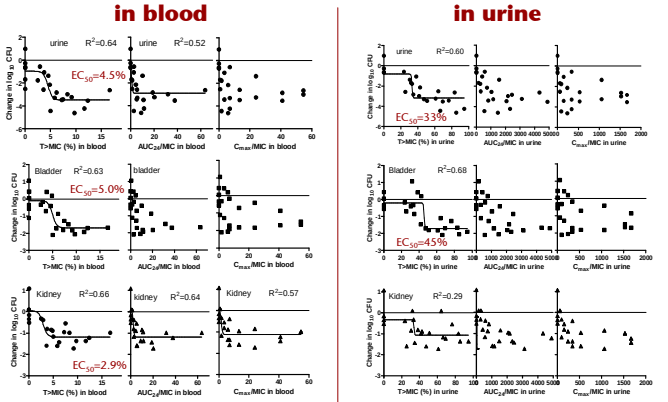
Cpeak



AUC_{24}



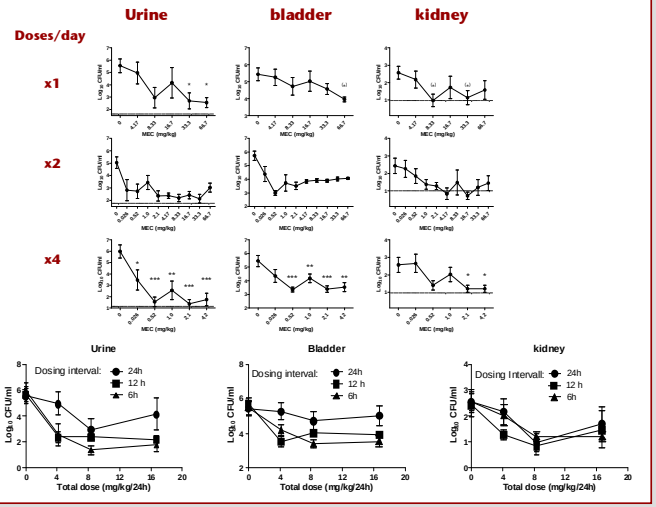
Correlation of MEC PK-PD indices



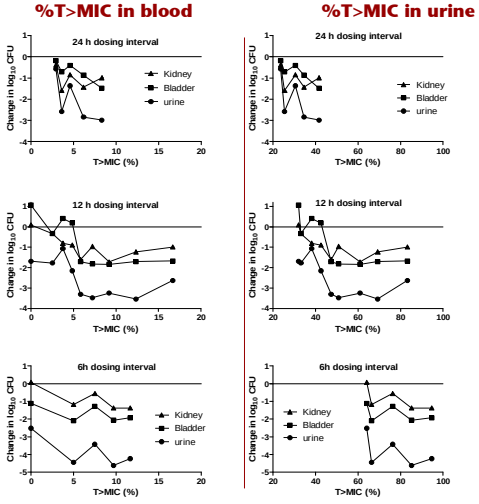
Maximal effect on bacterial reduction:

- in urine was achieved at 7.9 % T>MIC in blood, corresponding to 37% T>MIC in urine
- in bladder was achieved at 7.2 % T>MIC in blood, corresponding to 48% T>MIC in urine
- in kidney was achieved at 5.5 % T>MIC in blood

Relationship between dosing interval and efficacy



Relationship between T>MIC and efficacy



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