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THE CHOICE OF MURINE INFECTION MODEL AND THE IMMUNE STATUS OF THE MICE HAS AN IMPACT ON THE PHARMACODYNAMICS OF DICLOXACILLIN AGAINST STAPHYLOCOCCUS AUREUS INFECTION

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BACKGROUND

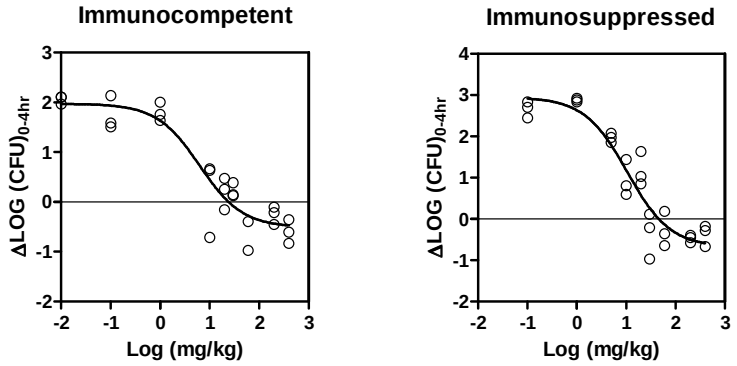
Murine infection models are useful tools in pharmacokinetic (PK) and pharmacodynamic (PD) studies of antibiotics. In this study we compared the peritonitis model to the thigh infection model and the impact of immunosuppression on the sensitivity of the infection models in determining PD parameters for dicloxacillin.

MATERIALS AND METHODS

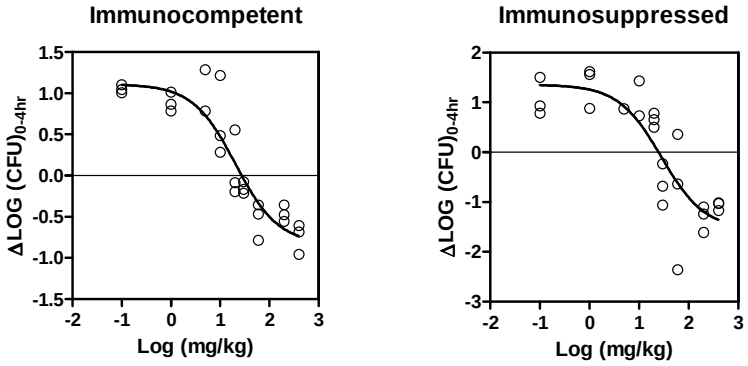
NMRI mice were immuno-suppressed with cyclopho-sphamide at day 4 and 1 before inoculation. Immunosuppressed mice or immuno-competent mice were then inoculated with *S.aureus* (clinical isolate E19977) either intraperitoneally or intramuscularly. At one hour post infection, mice were treated subcutaneously with a single dose of dicloxacillin ranging from 0.1 to 400 mg/kg (n=3 for each treatment group). The bacterial loads in the peritoneum or the thigh were determined at 4 hours post treatment. The $\log_{10}$ CFU level at start of treatment, the total increase of $\log_{10}$ CFU levels (Emax) and the half max effective dose (ED50) was calculated for each of the four infection models.

DOSE RESPONSE WITH DICLOXACILLIN AGAINST S.AUREUS

PERITONITIS MODEL



THIGH INFECTION MODEL



ED50 for Dicloxacillin in 4 different infection models

PERITONITIS MODEL

Immunocompetent: **6.75 ± 1.6**
Immunosuppressed: **10.6 ± 1.3**

THIGH INFECTION MODEL

Immunocompetent: **20.6 ± 1.3**
Immunosuppressed: **28.2 ± 1.6**

CONCLUSION

The murine peritonitis model resulted in a lower ED50 value for dicloxacillin than the thigh model regardless of immune status of the mice, indicating that the peritonitis model is more sensitive to antibiotic treatment of S.aureus infections. Further, the immuno-competent variants resulted in lower ED50 values than the corresponding immuno-suppressed model, indicating that an intact immune system contributes to the effect of the antibiotic. Thus, the choice of infection model will have an impact in the PKPD results, and this may especially be of importance when extrapolating PKPD parameters to human infection.

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