Interspecies variability in antibiotics protein binding and bacterial growth *in-vitro* as basis for translational PK/PD studies

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Background

PPB plays a pivotal role in deciphering key properties of drug candidates. Animal models are generally used in preclinical development of new drugs to predict their effects in humans using translational PK/PD. Interspecies differences in protein binding and bacterial growth in the central compartment is often neglected. Thus, we compared protein binding of cefazolin and clindamycin as well as bacterial growth of different pathogens *in vitro*.

Methods

The protein binding (PB) extent of cefazolin and clindamycin was studied in human, bovine and rat plasmas at different concentration in buffer and media containing 20 to 70% plasma or pure plasma. For UF, centrifugation technique was used to determine PB. Similarly, PPB of cefazolin and clindamycin was estimated using ED, where two cells separated by a semipermeable membrane were equilibrated at 37 °C for 4 hours and total compound concentration (bound/free) was determined. Moreover, bacterial growth was performed in MHB containing various amounts of plasmas.

Results

The pattern for cefazolin binding to plasma proteins was found to be similar in both UF and ED. There was a significant decrement in cefazolin binding to the bovine plasma as compared to human plasma (Figure 1), whereas the pattern in rat plasma was more or less consistent with that in human for cefazolin (Figure 1). Interestingly, we could witness a significant decrease in binding of clindamycin to the rat plasma as compared to the human plasma, and the pattern in bovine plasma was more or less consistent with that in human for clindamycin. Moreover, our growth curve analysis revealed considerable growth inhibition of *S. aureus* ATCC 29213 at 70% bovine or rat plasma as compared with 70% human plasma or pure MHB after 24 hours.

Conclusion

Our study highlights the interspecies differences regarding PK (differences in the unbound fraction) and PD (differences in bacterial growth). These finding need to be taken into account

before preclinical PK/PD data are extrapolated to human patients. Studies investigating the impact on antimicrobial activity in plasma of different species are ongoing.

Figure 1: Plot (mean ± SD) of PPB percentage of cefazolin of human (grey), bovine (purple) and rat (green) plasmas at different cefazolin concentrations using ultrafiltration (A) and equilibrium dialysis (B). The experiments were performed in triplicates.