Analysis of ceftolozane pharmacokinetics in a porcine model of mechanical ventilation and severe pneumonia

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BACKGROUND

Ceftolozane (Fig. 1) is a new cephalosporin that exhibits time-dependent killing activity against Gram-negative organisms, including *P.aeruginosa*.

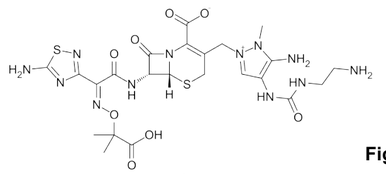

Figure 1

Ceftolozane pharmacokinetics (PK) have been evaluated in healthy humans. Standard dosing is ceftolozane/tazobactam IV 2000/1000 mg every 8 hours for severe pneumonia. Yet, ceftolozane PK in critically ill patients are not fully elucidated. Thus, animal models of critical illness are needed to comprehensively characterize pharmacokinetics of this drug.

AIMS

We tested, in an animal model of mechanical ventilation and severe pulmonary infection, different dosages of ceftolozane to achieve epithelial lining fluid (ELF) concentration-time curve from 0 to 8 h post-dose (AUC_{0-8}) of 150 µg*h/mL, as currently recommended in humans[1].

MATERIALS AND METHODS

6 pigs (weight 30-35 Kg) mechanically ventilated. Following surgical preparation, we administered intravenously (IV) 30mg/Kg of ceftolozane, over a 60-minute period; in 2 animals we administered 60mg/Kg IV. In 2 additional animals, we developed severe P.aeruginosa pneumonia[2]; then, we administered 60mg/Kg of ceftolozane IV. Plasma samples were collected before drug administration and at 1, 2, 4, 6, 8, 12, and 24 h thereafter. Bronchoalveolar lavage (BAL) sampling was performed before drug administration and at 1, 4, 8, 12, and 24 h thereafter. Concentrations of ceftolozane/tazobactam in plasma and BAL fluids were quantified through high-performance liquid chromatography. Plasma and BAL urea concentrations were assayed. Finally, ELF concentrations and AUC_{0-8} were computed using standard formulae.

Supported by:

RESULTS

Figure 2. Mean concentration-time profiles of Ceftolozane in plasma

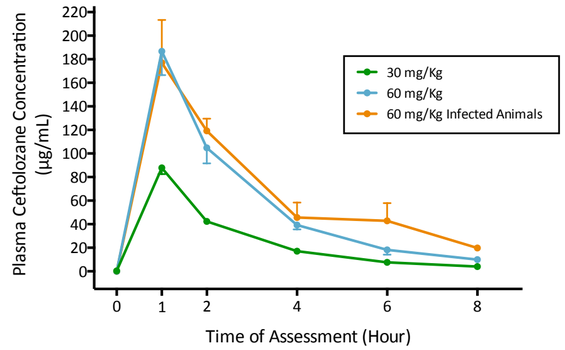

Figure 3. Mean concentration-time profiles of Ceftolozane in ELF

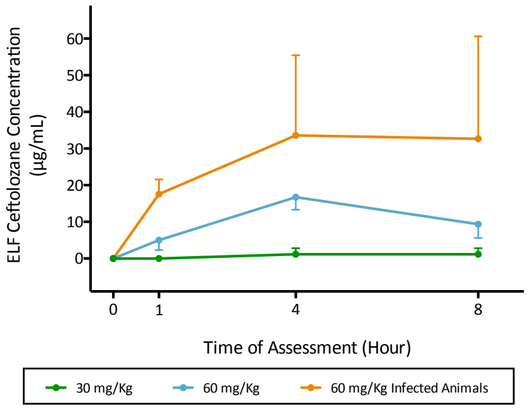

Figure 4. Plots of mean (+standard deviation[SD]) AUC_{0-8} of Ceftolozane

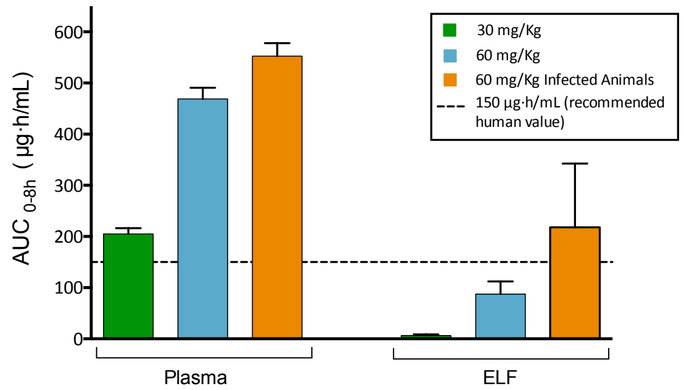

Table 1. Pharmacokinetic parameters of Ceftolozane after single dose

	30 µg/ml	60 µg/ml	60 µg/ml Infected animals
Plasma			
Cmax (µg/mL)	87.8 ±5.29	186.74±20.23	177.05±36.35
T max (h)	1	1	1
MRT (h)	3.41±0.47	3.20±0.1	3.77±0.28
ELF			
Cmax (µg/mL)	1.15±1.63	16.74±3.42	33.60±21.87
T max (h)	1	4	4
ELF penetration (%)	3.1	18.6	39.4

Cmax, maximum plasma/ ELF concentration; Tmax, time of maximum plasma/ ELF concentration; MRT, mean resident time

CONCLUSIONS

Based on our preliminary results, a dose between 30 and 60 mg/Kg of ceftolozane should be administered intravenously to achieve an ELF AUC0-8 of 150 µg*h/mL. Further studies are currently undergoing to achieve these endpoints and to test therapeutic efficacy of ceftolozane in severe P. aeruginosa pneumonia.

References:
1. Xiao AJ, et al. J Clin Pharmacol 2015; 56(1) 56-66
2. Luna CM, et al. Chest 2007; 132:523-31