P1313
Paper Poster Session
New antibiotics against Gram-negative bacteria

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

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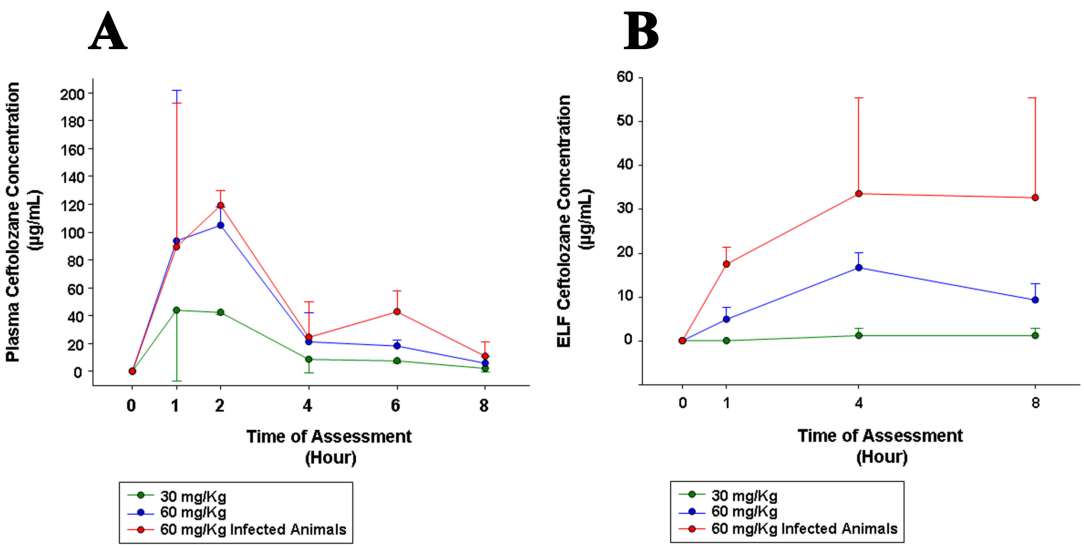
Background: Ceftolozane/tazobactam is a novel cephalosporin with a well established beta-lactamase inhibitor that exhibits time-dependent bactericidal activity against Gram-negative organisms, including *P.aeruginosa*. Ceftolozane/tazobactam pharmacokinetics (PK) have been evaluated in healthy humans and patients with bacterial infections. Yet, ceftolozane/tazobactam PK in critically ill patients are not fully elucidated. Thus, animal models of critical illness are needed to comprehensively characterize this drug. We tested, in a porcine model of mechanical ventilation and

severe pulmonary infection, different dosages of ceftolozane/tazobactam to achieve ceftolozane epithelial lining fluid (ELF) concentration-time curve from 0 to 8 h (AUC_{0-8}) of 150 µg*h/mL, as currently recommended in humans (Xiao AJ et al: *J Clin Pharmacol* 2015).

Material/methods: 6 female pigs (weight 30-35 Kg) were anesthetized, tracheally intubated and mechanically ventilated. Following surgical preparation, in the first two animals, we administered intravenously (IV) 30mg/Kg of ceftolozane, over a 60-minute period. Then, in 2 animals we administered 60mg/Kg IV. Finally, in the last 2 animals, we developed severe *P.aeruginosa* pneumonia (Luna CM et al *Chest* 2007;132: 523-31); then, we administered 60mg/Kg of ceftolozane IV. Plasma samples were collected before drug administration and at 1, 2, 4, 6, 8 h thereafter. Moreover, bronchoalveolar lavage (BAL) sampling was performed before drug administration and at 1, 4, 8h thereafter. Concentrations of ceftolozane in plasma and BAL fluids were quantified through high-performance liquid chromatography. Plasma and BAL urea concentrations were assayed. Finally, ELF concentrations were computed using standard formulae. Plasma and ELF AUC_{0-8} were computed.

Results: In figure 1A, mean±SD plasma concentrations for different dosages of ceftolozane and clinical conditions are reported. Whereas, in figure 1B, mean±SD ELF concentrations are depicted (N:2, per each time of assessment). Thus, in pigs undergoing treatment with 30 and 60 mg/Kg of ceftolozane, and 60 mg/Kg during severe pneumonia, plasma AUC_{0-8} were 204.8±11.4, 468.9±21.6 and 552.5±25.3 µg*h/mL, respectively. Whereas, the ELF AUC_{0-8} were 6.3±2.4, 87.3±24.9 and 218.1±124.5 µg*h/mL, respectively. As a result, ELF ceftolozane penetrations were 3.1, 18.6 and 39.4%, respectively.



Conclusions: Based on these preliminary results, in a porcine model of mechanical ventilation and severe pneumonia, a dose slightly less than 60 mg/Kg of ceftolozane IV should be administered to achieve an ELF AUC_{0-8} of 150 µg*h/mL. Further studies are currently undergoing to achieve these endpoints and to test therapeutic efficacy of ceftolozane/tazobactam in severe *P.aeruginosa* pneumonia.