Efficacy of Imipenem and Tigecycline in a Mouse Pneumonia Model Infected with Acinetobacter baumannii

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Abstract

Background: A. baumannii (ABAU) is the most dominant pathogen currently, associated with nosocomial pneumonia and bacteremia infections. Data is crucial for evaluating new agents. We have previously evaluated ABAU clinical isolates in acute pneumonia models to assess anti-pneumonia efficacy. This study identifies whether the infection model is appropriate for these agents.

Methods: Female CD-1 mice were rendered neutropenic by dosing Cytoxan (150/100 mg/kg at 8/4 hours) and challenged intranasally with ABAU clinical isolates at 5.1 – 6.9 log CFU/mL. For CFU studies, single inocula doses were administered intraperitoneally (i.p.) 4 hours after infection. Animals were monitored for up to 3.5 days for survival. For CFU counts, lungs were harvested 28 hours post-infection. For MICs, a panel of 28 clinical isolates from ABAU strains (UNT091-1 and UNT092-1) were selected for this study. The panel of clinical isolates was determined to be metabolically active and growing infection was generated in mice when studied, which would allow us to evaluate the MIC values determined by the broth dilution method according to CLSI guidelines. A. baumannii reference strain ATCC19606 was included as a quality control for each MIC test (data not shown).

Introduction

Antibiotic-resistant Acinetobacter baumannii infections have become a major concern in healthcare facilities in the United States. The need for effective treatments to these pathogens is critical. Here we describe the use of this model to evaluate the efficacy of Tigecycline against A. baumannii pneumonia infections.

Methods and Materials

Minimum inhibitory concentration (MIC): MICs were determined for Imipenem and Tigecycline against A. baumannii clinical isolates using broth dilution method according to CLSI guidelines. A. baumannii reference strain ATCC19606 was included as a quality control for each MIC test (data not shown).

Antibiotic Treated Mice vs. 28-Hour Controls

Panels 1, 3: Mean Log_{10} CFU Reduction (%) in Lungs of Antibiotic Treated Mice vs. 28-Hour Controls

Panel 2: Lung CFUs of UNT091-1 and UNT092-1 4 and 28 Hours Post-Infection

Panel 4: Mean Log_{10} CFU Reduction of UNT092-1 in the Lungs of Antibiotic Treated Mice vs. 28-Hour Controls

Panel 5: % Survival of Mice having Lethal Pneumonia Infections with UNT091-1

Panel 6: % Survival of Mice having Lethal Pneumonia Infections with UNT092-1

Summary and Conclusions

2. Minimum inhibitory concentration (MIC) values indicated that both A. baumannii clinical isolates (UNT091-1 and UNT092-1) were sensitive to Tigecycline (Panel 1). However, MIC values for Imipenem against ABAU clinical isolates varied. Higher dosages of Imipenem were needed to treat the clinical isolates resulting in limited survival over 3.5 days of dosing.

3. Tigecycline CFUs of UNT091-1 increased from 7.53 log_{10} CFU/mL at 4 hours post-injection to 8.55 log_{10} CFU/mL at 28 hours, while lung results for UNT092-1 increased from 7.28 log_{10} CFU/mL at 4 hours to 9.29 log_{10} CFU/mL at 28 hours. Single doses of Tigecycline at 12.5 – 50 mg/kg successfully reduced total lung counts for both stains, while single doses of Imipenem (12.5 mg/kg) increased total lung CFU counts for both strains. Multiple doses of Tigecycline over 3.5 days reduced total lung counts for both stains that ranged from 0.5 to 2.3 log_{10} CFU/mL when compared to 28-hour controls. For mice infected with UNT091-1, single doses of Tigecycline at 12.5 mg/kg resulted in 40% to 100% survival of mice surviving a lethal respiratory infection caused by UNT091-1. The same dose of Tigecycline (12.5 mg/kg) resulted in 100% survival of mice infected with UNT092-1. These results suggest that this model can be useful for evaluating new antibiotics to treat ABAU pneumonia infections.

References


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