INTRODUCTION

Community-acquired bacterial pneumonia (CABP) is one of the most common infections worldwide in humans (5-10 million cases and 1.1 million hospitalizations in US annually) which causes significant morbidity and mortality. Despite a number of antibiotics available to treat this infection, new antibacterial agents are needed to overcome resistance. BC-3781 is a novel, systemic pleuromutilin (mollicute and clostridial) with a spectrum of activity consistent with the organisms typically responsible for CABP such as Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus. Chlamydia pneumoniae and Mycoplasma pneumoniae pneumoniae have been shown to grow within the lung and favorable efficacy in murine pneumonia models suggesting further potential for the treatment of CABP.

A factor related to good tissue penetration is the intracellular accumulation of antibiotics in macrophages. Accumulation of drugs within polymorphonuclear cells and partitioning into various intracellular compartments can lead to improved distribution into the tissue surrounding the site of infection. This study investigated the accumulation of BC-3781 in macrophages in comparison with amoxicillin.

RESULTS

BC-3781 Uptake in Macrophages

- The intracellular concentration and accumulation of test compounds within the murine J74 macrophages is shown in Figure 2. BC-3781 showed approximately 30- to 50-fold accumulation in the macrophages at extracellular concentrations (Ce) of 1 µg/mL and 5 µg/mL after 5 h of incubation. The BC-3781 uptake appeared to be a fast process since significant Ci of approximately 35 µg/mL (Ce, 1 µg/mL) and 220 µg/ml (Ce, 5 µg/mL) were reached already at 1 h, corresponding to Ci/Ce ratios of ~30-40.

Effect of Lung Surfactant on the BC-3781 In Vitro Activity

- Checkboard experiments showed that bovine lung surfactant (Survanta™) had no effect on the MIC of BC-3781 in murine macrophages (Figure 2A). None of the eight isolates tested had an increase in BC-3781 MIC that was more than 2-fold at any Survanta™ concentration (Table 1). None of the eight isolates tested had an increase in BC-3781 MIC that was more than 2-fold at any Survanta™ concentration (Table 1). None of the eight isolates tested had an increase in BC-3781 MIC that was more than 2-fold at any Survanta™ concentration (Table 1). None of the eight isolates tested had an increase in BC-3781 MIC that was more than 2-fold at any Survanta™ concentration (Table 1).

CONCLUSIONS

- BC-3781 displayed a rapid 30- to 50-fold accumulation into murine macrophages dependent on the time of incubation at clinically relevant extracellular concentrations.

1. The antibacterial activity of BC-3781 was evaluated by checkerboard broth microdilution technique according to CLSI M100-S22 using an inoculum of 5x10⁶ CFU/mL and the following growth media: CAMHB for S. pneumoniae and M. catarrhalis, RPMI for S. aureus and S. epidermidis, and BHI for E. coli. Additional supplements were taken at t = 0 for determination of Ce and for proof of compound stability during the time period.

2. The MIC of BC-3781 and daptomycin in presence of 15-1000 µg/ml bovine lung surfactant (Survanta™, Abbot) was evaluated by the checkerboard broth microdilution technique according to CLSI M100-S22 using an inoculum of 5x10⁶ CFU/mL and the following growth media: CAMHB for S. pneumoniae, M. catarrhalis, and E. coli. BC-3781, Ce= 5 µg/ml, Azithromycin, Ce= 1 µg/ml, Penicillin G, Ce=1 µg/ml, Daptomycin, Ce= 1 µg/ml, Amoxicillin, Ce= 2 µg/ml, Gentamicin, Ce= 1 µg/ml, Rifampicin, Ce= 1 µg/ml, Ciprofloxacin, Ce= 1 µg/ml, Tobramycin, Ce= 1 µg/ml, and Streptomycin, Ce= 1 µg/ml.

REFERENCES


