Abstract

Background. Radezolid (RAD) is a novel biaryloxazolidinone in clinical development with broad spectrum of coverage with increased activity against MRSA, VRE, and four of S. aureus and four coagulase negative staphylococci (CONS) with differing susceptibilities. Its sequestration away from the lysosomes (not the mitochondria) of eukaryotic cells. Its sequestration away from the mitochondria is believed to be responsible for the late killing kinetics and the post-antibiotic effect (PAE) of oxazolidinones. RAD exhibits a broad spectrum of activity against a wide range of Gram-positive, Gram-negative bacteria, and anaerobes. Previous studies have shown that RAD is active against methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-intermediate Staphylococcus aureus (vSSI) and vancomycin-resistant enterococci (VRE).

The current study tests the PAE of RAD against eight staphylococcal species, four S. aureus and four coagulase-negative staphylococci with differing susceptibilities. The PAE was defined according to Craig and Gudmundson (5) as the time that bacterial counts after antibiotic exposure were equal to or lower than 1/100 of pretreatment levels.

Methods

Bacteria and Drugs

Eight staphylococcal species were obtained from American Type Culture Collection (ATCC) and the Clinical Infections Laboratory at Hershey Medical Center (HMC). Radzolid (RAD) and linezolid (LZD) were obtained from Rib-X Pharmaceuticals Inc., New Haven, CT.

MIC Methodology

MICs were determined by broth dilution methodology, with Mueller-Hinton broth (MHB) (6). MICs among S. aureus isolates ranged 0.5 - 4 µg/ml and 0.25 - 1 µg/ml for coagulase negative staphylococci (CONS). The MICs for the oxazolidinone-resistant strains were determined before exposure and immediately after dilution (0 h), and then every 2 h. The MIC was defined as the lowest concentration that inhibited bacterial growth. Results RAD MICs ranged from 0.25 to 4 µg/ml for S. aureus and from 0.5 to 256 µg/ml for CONS. DAP MICs among S. aureus isolates ranged 0.5 - 4 µg/ml and 0.25 - 2 µg/ml for coagulase negative staphylococci (CONS). The MICs were similar. Duration of the RAD PAEs varied between the same or increased slightly, after increasing exposure concentration. Against S. aureus ATCC 29213, RAD produced longer PAEs than LZD. Results were more active than LZD with MICs 1-6 times lower among staphylococci. RAD PAEs were similar or longer than those previously reported for linezolid.

Introduction

Radezolid (RAD) is a novel biaryloxazolidinone in clinical development. RAD exhibits a broad spectrum of coverage with increased activity against MRSA, VRE, and four coagulase negative staphylococci (CONS). Recent susceptibility testing against 90 linezolid-resistant clinical isolates has produced longer PAEs than LZD. Against the highly resistant S. aureus strain (CN338), RAD was highly potent with an MIC >16 times lower than linezolid (LZD).

Results

RAD PAE against S. aureus and coagulase negative staphylococci were generally similar. The PAEs of RAD were compared to those of LZD for S. aureus and four coagulase-negative staphylococci for uncomplicated skin and skin structure infections and a Phase 2 trial for community-acquired pneumonia (CAP).

The post-antibiotic effect (PAE) is a pharmacodynamic parameter used to modify antimicrobial dosing regimens. A prolonged PAE suggests that lengthening the dosing interval should be possible without loss of clinical effectiveness (6). The current study tests the PAE of RAD against eight staphylococcal species, four S. aureus and four coagulase-negative staphylococci with differing susceptibilities.

Conclusions

• For each isolate, RAD MICs compared to LZD were 2 to 16 times lower among S. aureus and 2 to 16 times lower among coagulase-negative staphylococci.

• Against the highly resistant S. aureus strain (CN338), RAD was highly potent with an MIC >16 times lower than linezolid (LZD).

• The length of the PAEs produced by RAD against all strains ranged from 0.4 h to 3.5 h.

• For strain ATCC 29213, the PAEs for RAD were 3 times (at 2 µg/ml) and 2.3 times (at 10 µg/ml) longer than those of linezolid.

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References