In Vitro Activity of Tebipenem (SPR859) Against Penicillin-Binding Proteins of Gram-Negative Bacteria

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ABSTRACT
Background: Carbapenems are potent antibacterial agents with broad spectrum activity. SPR859 is the microbiologically active form of the tebipenem-pivoxil prodrug SPR946, an orally available carbapenem with activity against extended spectrum β-lactamases (ESBL) producing Enterobacteriaceae.

In this study, SPR859 was characterized in vitro by assessing its potency against putative target penicillin-binding proteins (PBPs) and other antibiotics.

RESULTS

Carbapenems are potent antibacterial agents with broad spectrum activity [1]. SPR859 is the microbiologically active form of the tebipenem-pivoxil prodrug SPR946, an orally available carbapenem with activity against extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae.

In this study, SPR859 was characterized in vitro by assessing its potency against putative target penicillin-binding proteins (PBPs).

METHODS

PBPs were labeled using fluorescent Bocillin FL (BoFL) [2]. The binding affinity of β-lactamases (SPR859, meropenem [MEM], ceftazidime [CAZ], mezlocillin [MEC]) for PBPs was measured by adding increasing concentrations of the test drugs to membrane preparations of Escherichia coli K12 and Klebsiella pneumoniae ATCC 13883. The concentration of the drugs needed to block 50% of the binding of BoFL to each PBP (IC50) was estimated by quantification of fluorescence after gel electrophoresis. MICs were also determined by a broth microdilution technique according to CLSI guideline M7-A10 and in changes in bacterial cell morphology in presence of MICs to be recorded by microscopic examination after a 4 h exposure to the antibiotics.

RESULTS

The MICs for SPR859 and MEM against E. coli were correlated with their high affinity for PBP2 (SPR859 MIC: 0.015-0.03 µg/mL, MEM MIC: 0.015-0.03 µg/mL). MEM showed high binding to PBP2 (MIC 0.15-0.3 µg/mL) and CAZ had the highest affinity for PBP2 (MIC 0.35 µg/mL, IC50 0.011 ± 0.023 µg/mL). SPR859 and MEM also had good binding to PBP7 (IC50 0.058 ± 0.28 µg/mL, and 0.45-0.54 µg/mL, respectively). Binding to PBPs 1b and 2a was equivalent for CAZ, SPR859 and MEM (IC50 range 0.25-0.35 µg/mL), but CAZ had no significant binding to PBPs 4 and 5/6 (IC50 >20 µg/mL) compared to SPR859 and MEM (IC50 range 0.25-2.12 µg/mL). K. pneumoniae PBPs and PBPs 2b and 3 were also the primary targets of SPR859, with IC50 values similar to those determined for these PBPs in E. coli. As expected for β-lactam antibiotics having high affinity for PBPs, exposure to SPR859, MEM and MEC caused rounding of cells, whereas preferential binding to PBP2 by CAZ provoked cell filamentation.

Conclusion: SPR859 was found to be a potent inhibitor of multiple PBPs, and a primary PBP2 inhibitor, similar to other carbapenems in this class. This data suggest further clinical development of SPR946 to become the first oral carbapenem for treatment of serious Gram-negative infections.

IOINTRODUCTION

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REFERENCES


ACKNOWLEDGMENTS

This study was supported by a research contract between Université de Sherbrooke and Spero Therapeutics Inc. This work was also supported by a grant from the Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT) to F. Malouin.

E. Lacasse received a studentship from FQRNT.