Potentiation of cefepime by the boronate VNRX-5133 versus gram-negative bacteria with known β-lactamases

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Background

Boronates, like diazabicyclooctanes, are of major interest as a new-class of β-lactamase inhibitors (BLIs). The sole marketed boronate, vaborbactam, only inhibits KPC carbapenemases, but experimental molecules have broader spectra. We evaluated one novel boronate BLI, VNRX-5133 (VenatoRx) in combination with cefepime against gram-negative bacteria with known β-lactamases (BLs).

Methods

Isolates were selected from among submissions to the UK reference laboratory. BL genes were identified by PCR or sequencing and MICs were determined by CLSI agar dilution.

Results

VNRX-5133 lacked antibacterial activity, with MICs >32 mg/L for all species. For control Enterobacteriaceae, lacking BLs, the geometric mean (GM) MICs of cefepime (0.05 mg/L) was little affected by addition of VNRX-5133 8 mg/L, falling to 0.04 mg/L. This differential was greatly increased for cefepime-resistant isolates with KPC carbapenemases (GM MIC cefepime reduced from 24.8 mg/L to 0.16 mg/L by VNRX-5133 at 8 mg/L), VIM carbapenemases (15.2 mg/L to 0.23 mg/L), NDM carbapenemases (104 mg/L mg/L to 2.9 mg/L), combinations of ESBL plus impermeability (93.8 to 1 mg/L) and AmpC plus impermeability (2.7 mg/L to 0.38 mg/L). Cefepime is rather stable to OXA-48-like enzymes and the GM MIC for ceftazidime-susceptible OXA-48 producers was reduced only from 1.3 to 0.14 mg/L; however, that for ceftazidime-resistant OXA-48 producers fell from 33.4 mg/L to 0.25 mg/L, putatively reflecting inhibition of co-produced ESBLs. Synergy for Enterobacteriaceae with IMP carbapenemases was minimal, with the GM cefepime MIC reduced only from 23.2 mg/L to 12.9 mg/L. Little potentiation was seen for *Acinetobacter* isolates with OXA-23,-24,-51 or -58 carbapenemases or for *P. aeruginosa* with NDM or VIM enzymes. Lesser potentiation against VIM-positive *P. aeruginosa* than VIM-positive Enterobacteriaceae likely reflects greater impermeability or efflux function. The GM MIC of cefepime for *Elizabethkingia* spp. was reduced from 21.1 to 3.5 mg/L and that for *S. maltophilia* from 24.3 to 5.3 mg/L.

Conclusions

VNRX-5133 has a broad potential to reverse cefepime non-susceptibility resistance-mediated by Class A, B (except IMP), C and D enzymes in Enterobacteriaceae. Its potential against non-fermenters was more limited, perhaps reflecting their greater impermeability and efflux function, but significant potentiation of cefepime was seen for *Elizabethkingia* spp. and *S. maltophilia*.

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