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P1536 Potentiation of cefepime by the boronate VNRX-5133 versus Gram-negative bacteria with known beta-lactamases

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Background: Boronates, like diazabicyclooctanes, are of major interest as new-class β–lactamase inhibitors. The sole marketed boronate, vaborbactam, only inhibits KPC carbapenemases, but experimental molecules have broader spectra. We evaluated one novel analogue, VNRX-5133 (VenatoRx) combined with cefepime against gram-negative bacteria with known β–lactamases. **Materials/methods:** Isolates were selected from among submissions to the UK reference laboratory; β–lactamase 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 β–lactamases, 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 anyway 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*.