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P1033 Nacubactam (RG6080) alone and in combination against metallo-beta-lactamase (MBL)-producing Enterobacteriaceae

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Background: Diazabicyclooctanes (DBOs) are promising β-lactamase inhibitors. A few, including nacubactam (RG6080/OP0595) also inhibit enterobacterial PBP2, achieving antibacterial activity and potentiating PBP3-targetted β-lactams; this can allow activity against strains with enzymes not inhibited by DBOs, including MBLs. We investigated the proportions of MBL-producing Enterobacteriaceae susceptible to nacubactam-β-lactam combinations.

Materials/methods: We examined (i) 158 Enterobacteriaceae with NDM carbapenemases and 52 with VIM carbapenemases, as consecutively referred by UK diagnostic laboratories – these were predominantly *Klebsiella* and *E. coli* and mostly had aztreonam cross-resistance, indicating ESBL co-production – and (ii) 99 selected MBL Enterobacteriaceae, chosen to also represent rarer MBLs and less-prevalent producer species along with aztreonam-susceptible producers. Isolates were identified by MALDI-ToF and MICs determined by CLSI agar dilution.

Results: MIC distributions of nacubactam, tested alone, were bimodal, largely clustering between 1-8 mg/L or >32 mg/L, with few values between these groups. For *E. coli* and *Enterobacter* over 85% of isolates fell into the 'low' MIC cluster whereas for Proteeae, almost all MICs exceeded 32 mg/L; for *Klebsiella* the low:high split was 35%:54% and MICs often were difficult to read, with considerable trailing. At 8+4 mg/L aztreonam-nacubactam inhibited 308/309 Enterobacteriaceae vs. 303/309 for aztreonam-avibactam 8+4 mg/L; proportions inhibited by cefepime-nacubactam 8+4 and meropenem-nacubactam 4+4 mg/L were 278/309 and 262/309, respectively, including 196/210 and 183/210, respectively among the consecutive MBL producers, which provide a nationally representative series. Cefepime-avibactam 8+4 mg/L and meropenem-avibactam 8+4 mg/L were active against just 68/309 and 85/309 MBL producers respectively, reflecting avibactam's lack of secondary activities. Among the most resistant isolates, comprising 28 *Klebsiella* spp. with nacubactam MICs >32 mg/L and both cefepime and meropenem MICs >128 mg/L, 15 were susceptible to cefepime-nacubactam 8+4 mg/L and six to meropenem-nacubactam 8+4 mg/L. Please copy and paste the corresponding text here

Conclusions: Nacubactam combinations, including those using β-lactams such as meropenem and cefepime that are not stable to MBLs, have wide activity against MBL producer *in vitro*. This behaviour substantially reflects the antibacterial activity of nacubactam itself but also, as illustrated with the highly nacubactam-resistant strains, nacubactam's enhancer activity.