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O1061 Pharmacodynamics of VNRX-5133 in combination with cefepime studied in an *in vitro* model of infection

Alan Noel[1], Karen E. Bowker*[1], Marie Attwood[1], Alasdair P. Macgowan[1]

[1] BCARE, North Bristol NHS Trust

Background: VNRX-5133 (VNRX) is a novel β-lactamase inhibitor with activities against serine and metallo β-lactamases, being developed with cefepime (CEF). The objective was to define the pharmacodynamics (PD) of VNRX against Enterobacterales with KPC, AmpC, OXA-48 and CTX-M β-lactamases.

Materials/methods: An *in vitro* one compartment dilutional pharmacokinetic model was used. Free drug serum concentrations associated with CEF 2G by 2hr infusion 8hrly were simulated and VNRX given by continuous infusion - concentration range 0.003mg/L-10mg/L. VNRX was then fractionated at three exposures across the response relationship. Reduction in viable count at 24h (log CFU/mL, d24) was the primary end point. Four clinical strains were used: *K. pneumoniae* (KP) expressing KPC (CEF/VNRX MIC 1mg/L); KP OXA-48 (CEF/VNRX MIC 2mg/L); *E. coli* (EC) CTX-M (CEF/VNRX MIC 0.25mg/L) and EC AmpC (CEF/VNRX MIC 8mg/L).

Results: In VNRX continuous infusion experiments, ≥4 log kill was attained with VNRX concentrations of >0.01mg/L against CTX-M–producing *E.coli;* ≥0.5mg/L against KPC-producing and OXA-48-producing KP; and ≥4mg/L against AmpC-producing *E.coli*. Combined analysis of the continuous infusion and dose fractionation simulations were conducted to determine the VNRX pharmacokinetic driver (AUC, Cmax, Time > threshold) for each strain. For the KPC-producing KP, AUC (R^2 0.696) and T>0.25mg/L VNRX (R^2 0.718) were best related to d24. For the OXA-48 producer, AUC (R^2 0.672) and T>0.25mg/L (R^2 0.941) were best related to d24. For EC producing CTX-M, AUC (R^2 0.744) and T>0.5mg/L (R^2 0.616) using a 10^8 CFU/mL inoculum were best related to d24. Finally, for AmpC producing EC, AUC (R^2 0.642) and T>2mg/L (R^2 0.520) were best related to d24. The VNRX AUC to produce a static effect at 24h with each strain was 4.0-5.8mg/L.h and a -1 log reduction in count 4.4-11.2mg/L.h. AUC/MIC, Cmax/MIC and T>MIC/4 could also be related to d24 in a pooled analysis including all four strains, however, curve fit was poor R^2<0.55.

Conclusions: VNRX was effective in combination with cefepime in producing bacterial clearance from the model for cefepime-resistant isolates of Enterobacterales with KPC, OXA-48, CTM-X and AmpC enzymes. The primary pharmacodynamic driver is AUC or time over threshold - both being closely related to antibacterial effect.