# A1-1383 Pharmacodynamics of Razupenem (PTZ601) against Enterobacteriaceae

50th ICAAC Meeting
Boston, MA
September 12-15, 2010

KE. Bowker, AR. Noel, SG. Tomaselli, HC. Elliott, AP. MacGowan
*BCARE, Department of Microbiology, North Bristol NHS Trust, Bristol, UK*

Corresponding author
alan.noel@nbt.nhs.uk

## Introduction

- Razupenem (RAZ) is an investigational parenteral methyl carbapenem active against MRSA and ESBL producing Enterobacteriaceae.
- $MIC_{90}$s for ESBL producing *E.coli, Klebsiella* spp and *Enterobacter cloacae* are 0.5, 0.2 and 8mg/L respectively.
- A 1g dose indicates a Cmax 57.8 mg/L after a 1h infusion with a t½ of 1.5h. Urinary excretion is 10-25% and volume of distribution 15L. Human plasma protein binding is 50%.
- T>MIC is the dominant pharmacodynamic (pD) index for razupenem.

- The aim of this study was to define the RAZ fT>MIC relationship to antibacterial effect (ABE) and emergence of resistance (EoR) for Enterobacteriaceae**.**

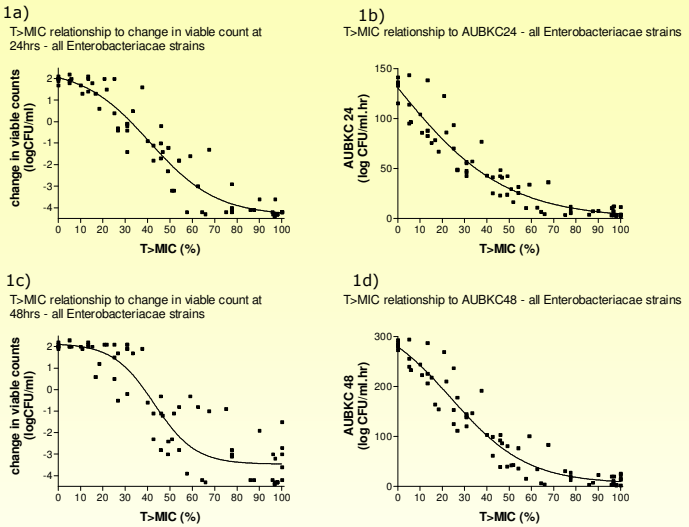
## Materials and methods

- An in vitro pK model was used to simulate RAZ exposures over the range 0-100%, T>MIC for 5 Enterobacteriaceae strains.
- A wild type, a CTX-M and a SHV-12 producing *E.coli* (raz MICs 0.03 - 0.1mg/L), and two *Enterobacter* spp RAZ MICs 0.4 (AmpC producing) and 6.0mg/L were used.
- ABE was assessed by changes in viable count at 24h and 48h (d24, d48) and EoR by changes in population analysis profiles (PAP) on plates containing x1, x2, x4, and x8 RAZ MIC.

## Results

- The relationship between fT>MIC and ABE is shown on Figures 1a-1d. Table 1 shows T>MIC values for the individual strains.
- The T>MIC for a 24h static effect, -1 log and -3 log reduction in count (mean ± SD, range) was: 34 ± 8, 27-47%, 42 ± 8, 34-55% and 61 ± 9, 52-74% respectively.
- The T>MIC for 48h static effect increased to 42 ± 5, 38-51%.
- T>MIC was related to the probability and degree of change in PAP (Figures 2a and 2b, Table 2).
- PAPs showed growth on MICx2, x4 and x8 recovery media at fT>MIC in the range 1-69%, but rarely at values of ≥70%.

Figures 1a-d: The relationship between T>MIC and antibacterial effect at 24 and 48h




Figures 2a and 2b: T>MIC relationship to growth on x2, x4 and x8MIC recovery plates after 24h (2a) and 48h (2b)

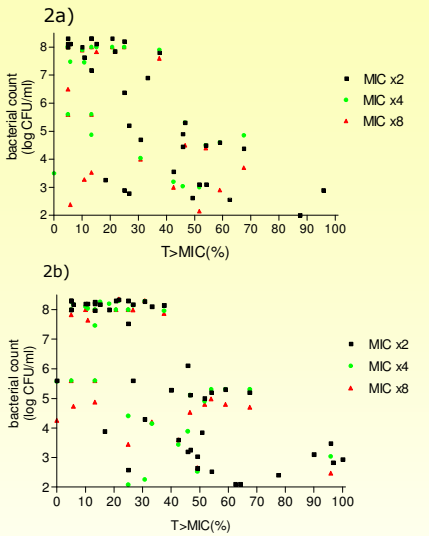



Table 1: T>MIC values for a static, -1, -2, -3 and -4 log reduction in viable count for each strain.

| | T>MIC% for | | | | | | |
|---|---|---|---|---|---|---|---|
| Strain | E.coli | E.coli | E.coli | Enterobacter | Enterobacter | Average | Pooled analysis |
| | SHV-12 | CTXM | AMPs | spp | spp | | |
| | 31053 | 35776 | 39136 | 35054 | 34425 | | |
| MIC (mg/L) | 0.09 | 0.1 | 1.2 | 0.4 | 6 | | |
| At 24hrs | | | | | | | |
| Static | 31.7 | 47 | 35 | 27.5 | 30.2 | 34.3 ± 7.6 | 32.4 |
| -1 | 40.9 | 55.5 | 40.9 | 34.2 | 40.9 | 42.5 ± 7.8 | 41.5 |
| -2 | 49.7 | 64.1 | 46.7 | 42.3 | 50.3 | 50.6 ± 8.2 | 50.5 |
| -3 | 61.7 | 74 | 52.6 | 52.3 | 63.1 | 60.7 ± 8.9 | 61.5 |
| -4 | 92.6 | 89.4 | 63.6 | 87.9 | 83.2 | 83.4 ± 11.5 | 83.9 |
| At 48hrs | | | | | | | |
| Static | 39.8 | 50.6 | 44.8 | 37.6 | 38.3 | 42.2 ± 5.5 | 38.5 |
| -1 | 40.3 | 61.2 | 47.4 | 39.6 | 48.3 | 47.4 ± 8.7 | 45.2 |
| -2 | 40.9 | 71 | 50.6 | 41.6 | 59.1 | 52.6 ± 12.7 | 52.5 |
| -3 | - | 81.6 | 52.6 | 57 | 73.2 | 66.1 ± 13.6 | 64.9 |
| -4 | - | 95.4 | 58.4 | - | - | 76.9 - | - |

Table 2: Changes in razupenem population profiles at 48 h

| T>MIC range | Growth on MIC x2 plates | | Growth on MIC x4 plates | | Growth on MIC x8 plates | |
|---|---|---|---|---|---|---|
| | No. of exps with >2 log growth | Viable count (log CFU/ml) | No. of exps with >2 log growth | Viable count (log CFU/ml) | No. of exps >2 log growth | Viable count (log CFU/ml) |
| 1-9 | 4/4 (100%) | 8.2 ± 0.1 | 4/4 (100%) | 7.5 ± 1.3 | 4/4 (100%) | 6.5 ± 1.6 |
| 10-19 | 8/8 (100%) | 7.6 ± 1.5 | 7/8 (87%) | 7.7 ± 0.9 | 6/8(75%) | 7.1 ±1.4 |
| 20-29 | 7/7 (100%) | 7.0 ±2.2 | 6/7 (86%) | 6.5 ± 2.6 | 5/7 (71%) | 7.2 ±2.1 |
| 30-39 | 4/4 (100%) | 7.2 ± 1.9 | 4/4 (100%) | 5.7 ± 2.9 | 3/4 (75%) | 6.8 ±2.3 |
| 40-49 | 8/9 (89%) | 4.0 ±1.3 | 4/9 (44%) | 3.7 ± 1.0 | 3/9 (33%) | 3.6 ±0.9 |
| 50-69 | 8/10 (80%) | 3.9 ±1.5 | 4/10 (40%) | 5.2 ± 0.2 | 4/10 (40%) | 4.8 ±0.1 |
| ≥ 70 | 5/12 (42%) | 2.9 0.4 | 2/12 (17%) | 2.9 ±0.1 | 2/12 (17%) | 2.3 ±0.2 |

## Conclusions

- A RAZ T>MIC of 30-45% is associated with a 24h static to -1 log kill of Enterobacteriaceae.
- A T>MIC of >70% is required to suppress changes in PAPs at 24h.

Bristol Centre for Antimicrobial Research and Evaluation

North Bristol NHS Trust