A-024

The Pharmacodynamics of Doripenem Against *Pseudomonas aeruginosa* and *Acinetobacter* spp.

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Abstract

Background: Doripenem (dori) is a new parenteral carbapenem with broad in vitro potency against multiresistant Gram negative pathogens such as *P. aeruginosa* and *Acinetobacter* spp. (MIC_{50} 0.5 and 1 mg/L, respectively). The dori T>MIC relationship to antibacterial effect (ABE) and emergence of resistance (EoR) is not well studied for these species. We used an in vitro pharmacokinetic model (IVPKM) to examine the relationship of T>MIC to ABE and EoR.

Methods: A single compartment IVPKM was used to simulate dori dosing 8 hrly to produce a T>MIC range (0-100%). Two strains of *P. aeruginosa* (dori MIC 0.24 and 0.75 mg/L) and 3 strains of *Acinetobacter* (MICs 0.45, 0.75, and 3 mg/L) were used. The initial inoculum was 10^6 CFU/mL, experiments were performed over 48h, ABE was measured by log change in viable count at 24h (d24) and EoR by growth on MIC x4 and x8 plates at 24h dori exposure. T>MIC was related to d24 using a Sigmoid Emax model.

Results: The T>MIC for *P. aeruginosa* strains MIC 0.24/0.75 mg/L to produce a 24h static, -1, -2, -3 log drop in count was 37/24%, 42/29%, 47/34%, and 62/41%. EoR occurred only at T>MIC of ≤25%. For the 3 *Acinetobacter* strains (MIC 0.45, 0.75, 3 mg/L), the T>MIC for static, -1, -2, -3, log drop was: 20 ± 11, 25 ± 10, 33 ± 12, 52 ± 10, respectively. EoR, growth on MIC x4 and x8 plates, occurred at T>MIC of ≤25%.

Conclusions: For dori, a T>MIC of 20-45% is associated with a 1-2 log reduction in viable counts of *P. aeruginosa* and *Acinetobacter* spp. Risk of EoR is minimised if a T>MIC of >25 is maintained.

Introduction

- Doripenem is an injectable carbapenem. It has a trans-6-hydroxyethyl group protecting against β-lactamases and a 1-β-methyl group preventing inactivation by renal dehydropeptidases.
- Doripenem has a similar spectrum of activity to that of imipenem and meropenem, with the benefit of lower minimum inhibitory concentrations (MICs) to *Pseudomonas aeruginosa*.
- Doripenem MIC_{50}s for *P. aeruginosa* are in the range of 0.12-0.5 mg/L, with strains showing an average of -2 to -3 doubling dilution reduction of MIC with doripenem compared with imipenem.
- Doripenem MICs of *Actinetobacter* spp. are similar to those of imipenem, with less than a single tube doubling dilution between strains.
- Pharmacokinetics are linear, and a single intravenous (IV) 1-hour infusion of 500 mg gives a C_{max} of 20-25 mg/L and an AUC of 35-40 mg/L•h. The terminal half-life is about 1 hour, with most of the drug appearing unchanged in the urine. Protein binding is <10%.
- Free drug T>MIC (fT>MIC) is the dominant pharmacodynamic index for doripenem. In the murine thigh infection model, exposures of ~20% fT>MIC were associated with a 24-hour static effect, whereas exposures of >40% fT>MIC were associated with maximum killing.
- Doripenem is approved in the United States for complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). In Europe, doripenem is approved for cIAI and cUTI, as well as nosocomial pneumonia and ventilator-associated pneumonia.
- We used an in vitro pharmacokinetic model to perform a series of dose-ranging studies to define the fT>MIC correlation to antibacterial effect and emergence of resistance in strains of *P. aeruginosa* and *Acinetobacter* spp.

Methods

In Vitro Pharmacokinetic Model

- A single compartment dilutional in vitro model was used; 50% Mueller Hinton broth was pumped from a reservoir to the bacterial chamber via a peristatic pump at a flow rate of 231 mL/h. Doripenem was added at time 0, 8 hours, and 16 hours, and samples were taken hourly for viable count and confirmation of the concentration.

Bacteria

- Three strains of *P. aeruginosa* – doripenem, MIC 0.24 mg/L (strain 38475), MIC 0.75 mg/L (strain 39135), and MIC 3.0 mg/L (strain 17286).
- Three strains of *Acinetobacter* spp. – MIC 0.45 mg/L (strain 33980), MIC 0.75 mg/L (strain 28893), and MIC 3.0 mg/L (strain 7186).

Pharmacokinetics

- A range of pharmacokinetic profiles were simulated with each strain to produce a fT>MIC range from 0-100%. Doripenem was dosed in the model q8h at simulated human doses from 2440 mg to 5.9 mg. A minimum of 6 exposures was performed per strain. Doripenem was assayed by bioassay to confirm the simulated concentrations using *Escherichia coli* NCTC 10418 as the indicator organism, and the limit of detection was 0.25 mg/L.

Antibacterial Effect

- Experiments were performed with an initial inoculum of 10^6 colony forming units (CFUs)/mL. Simulations were performed over 48 hours. The antibacterial effect was determined by the log change in viable counts at 24 hours (d24) and the area under the bacterial kill curve, 0-24 hours (AUBKC24).

Emergence of Resistance

- Emergence of resistance was determined at 24 hours by culture from the model onto recovery media containing x1, x2, x4, and x8 MIC of the isolate under investigation. The correlation between T>MIC and antibacterial effect was delineated using a sigmoid Emax model.

Results

- For *P. aeruginosa*, the T>MIC correlation to d24 is shown in Table 1 and Figure 1. The correlation of T>MIC to AUBKC24 and growth on x4 MIC recovery plates are shown in Figure 2.

Table 1. Correlation Between T>MIC and d24 for Doripenem and *P. aeruginosa*

	Strain			
Strain MIC (mg/L)	38475 0.24	39135 0.75	17286 3.0	Mean ± SD
fT>MIC % for				
static effect	37	24	14	25 ± 11
-1 log drop	42	29	19	30 ± 11
-2 log drop	48	34	23	35 ± 13
-3 log drop	62	41	28	44 ± 17
R^2 model	0.92	0.94	0.96	

Figure 1. fT>MIC correlation to antibacterial effect for doripenem against *P. aeruginosa* measured by log change in viable count at 24 hours.

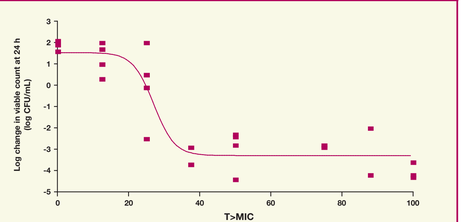
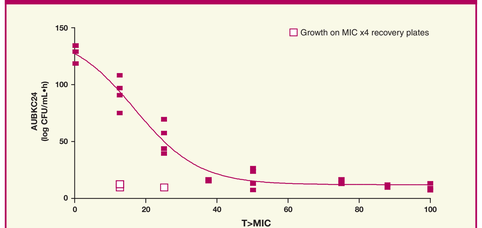


Figure 2. fT>MIC correlation to antibacterial effect and emergence of resistance for doripenem and *P. aeruginosa*.



- For *Acinetobacter* spp., the T>MIC correlation to d24 is shown in Table 2 and Figure 3. The correlation of T>MIC to AUBKC24 and growth on x4 MIC recovery plates are shown in Figure 4.

Table 2. Correlation Between T>MIC and d24 for Doripenem and *Acinetobacter* spp.

	Strain			
Strain MIC (mg/L)	33980 0.45	28893 0.75	7186 3.0	Mean ± SD
fT>MIC % for				
static effect	30	21	9	20 ± 11
-1 log drop	32	30	14	25 ± 10
-2 log drop	37	43	20	33 ± 12
-3 log drop	–	77	27	52
R^2 model	0.95	0.95	0.96	

Figure 3. fT>MIC correlation to antibacterial effect for doripenem against *Acinetobacter* spp. measured by log change in viable count at 24 hours.

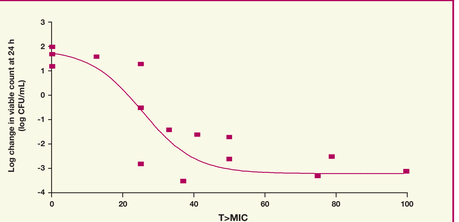
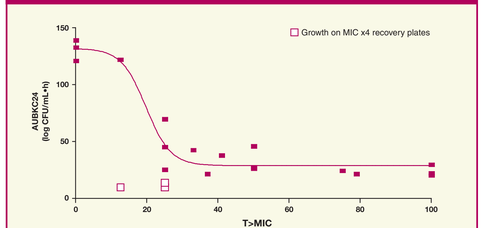


Figure 4. fT>MIC correlation to antibacterial effect and emergence of resistance for doripenem and *Acinetobacter* spp.



- The T>MIC and 24-hour bacteriostatic effect correlations are summarised in Table 3.

Table 3. Emergence of Resistance in *P. aeruginosa* and *Acinetobacter* spp. at 24 Hours

		fT>MIC %	
Strain	MIC (mg/L)	Static Effect at 24 Hours	Growth on MIC x4 Recovery Media
P. aeruginosa			
38475	0.24	37	12.5-25
39135	0.75	24	12.5
17286	3.0	14	12.5
Acinetobacter spp.			
33980	0.45	30	12.5-25
28893	0.75	21	25
7186	3.0	9	No growth

Conclusions

- The doripenem fT>MIC for a 24-hour static effect for *P. aeruginosa* was 25 ± 11% and for *Acinetobacter* spp. was 20 ± 11%. For both species, the maximum response occurred at fT>MIC of 40%-60%.
- Emergence of resistance occurred with all 3 strains of *P. aeruginosa* and 2 of 3 strains of *Acinetobacter* spp. Emergence of resistance occurred at fT>MIC of ≤25%.
- For doripenem, a fT>MIC target of 30%-40% is likely to be bactericidal against *P. aeruginosa* and *Acinetobacter* spp. while reducing the risk of emergence of resistance.

Poster presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting, October 25-28, 2008, Washington, DC.