PK-PD Evaluation of Doripenem (DOR) Against Extended Spectrum ß-Lactamase (ESBL) Producing Enterobacteraceae

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Abstract

BACKGROUND: **Increasing resistance among ESBL-producing bacteria is a growing concern. We examined the potential utility of DORI against ESBL-producing isolates.**

METHODS: **Physicians and house staff practicing in a 24-bed medical-surgical-trauma ICU are now required to A murine infection model was used to identify the PK-PD measure (T>MIC) associated with efficacy and the impact of ESBL production on the in vivo activity of DORI. Mice were infected with $10^{6.5\text{-}7.5}$ CFU/mL of 3 strains of E. coli (1 non-ESBL & 2 ESBL), 4 K. pneumoniae (2 non-ESBL & 2 ESBL), and 2 E. cloacae (1 non-ESBL & 1 ESBL). The T>MIC necessary to produce a static effect and a 1-log kill were determined using an Emax model. DOR MIC distributions for non-ESBL and ESBL producing E. coli, K. pneumoniae and P. mirabilis strains were determined by NCCLS methods. Mean parameter estimates and a covariance matrix from a population PK model were used for a 5000 patient Monte Carlo Simulation to estimate the probability of DOR attaining target exposure for a static/-log kill for various dosing regimens.**

RESULTS: **For a static effect, mean free drug T>MIC was 30% (20-38%) and 29% (26-33%) for non-ESBL and ESBL strains, respectively. For a 1-log kill, mean free drug T>MIC was 40% (27-47%) and 35% (30-39%) for non-ESBL and ESBL strains, respectively. The $MIC_{50/90}$ for combined non-ESBL (80) and ESBL (74) strains was ≤0.015/0.06 and 0.03/0.12, respectively. The table below demonstrates the impact of varying dose, interval, and infusion durations on PK-PD target attainment (%) at MICs of 0.12 and 0.25 mg/L.**

CONCLUSIONS: **ESBL production in the strains had no impact on the T>MIC needed for in vivo efficacy nor the DOR MIC distributions against Enterobacteraceae (p values 0.1-0.8). These data suggest that DOR may be useful for the treatment of infections caused by ESBL-producing bacteria.**

Dosing Regimen	MIC	Duration of Infusion (hours)	Percent of Patients Achieving T>MIC Target			
			35%T>MIC	40%T>MIC	45%T>MIC	50%T>MIC
125 mg q12h	0.12	1/2/3	100/100/100	94/100/100	41/94/100	3/39/95
250 mg q12h	0.12	1/2/3	100/100/100	100/100/100	99/100/100	76/99/100
500 mg q12h	0.12	1/2/3	100/100/100	100/100/100	100/100/100	0/0/10
125 mg q12h	0.25	1/2/3	70/99/100	9/69/100	0/8/74	0/0/10
250 mg q12h	0.25	1/2/3	100/100/100	94/100/100	41/94/100	3/39/95
500 mg q12h	0.25	1/2/3	100/100/100	100/100/100	99/100/100	76/99/100
250 mg q8h	0.25	1/2/3	100/100/100	100/100/100	100/100/100	100/100/100
250 mg q24h	0.25	24	98	98	98	98

Background

Increasing resistance among ESBL-producing bacteria is a growing concern. We examined the potential utility of doripenem against ESBL-producing and non-ESBL isolates. We defined the PK/PD parameter target necessary for efficacy in an animal infection model. We then considered human pharmacokinetics of doripenem with regard to this target using Monte Carlo simulation to estimate the upper limit MIC that one might expect to achieve this PK/PD target in the context of ESBL producing pathogens.

Methods

ORGANISMS AND IN VITRO SUSCEPTIBILITY TESTING

The study organisms and their MICs to Doripenem, Cefepime, Ceftazidime, and Cefotaxime are listed in Table 1. The mechanism of cephalosporin resistance was also determined and is listed in Table 1. MICs were determined in MHB by standard NCCLS microdilution techniques. All MICs were performed at least in duplicate. The gram-negative strains included ESBL producing isolates.

ANIMAL MODEL

Female Swiss ICR mice were used for all experiments. Neutropenia was produced by two injections of cyclophosphamide, 150 mg/kg 4 days prior to study and 100 mg/kg 1 day prior to study. The murine thigh-infection model was used for all studies. Approximately 10^6 cfu/ml of the study organisms were injected into both thighs two hours before starting therapy. The number of organisms in the thigh at the start of therapy varied from $10^{5.70}$ to $10^{7.68}$ cfu/thigh.

ANIMAL MODEL PHARMACOKINETICS

The pharmacokinetics of Doripenem were performed in thigh-infected neutropenic Swiss ICR mice. Drug doses of 9.38m 37.5, and 150 mg/kg were administered by subcutaneous injection of a 0.2 ml volume. Blood was removed from groups of three mice by retroorbital aspiration into heparinized capillary tubes at 0.25, 0.5, 0.75, 1, 1.5, 2, 3 and 4 hours after dosing. Doripenem plasma concentrations were measured using a microbiologic assay with S. aureus 6538p as the test organism. The lower limit of detection of Doripenem in the microbiologic assay was 0.12 µg/ml. The intra-day variation was less than 10%.

The half-life of Doripenem in individual mice was determined by linear least-squares regression. AUC was calculated by the trapezoidal rule from mean concentrations and extrapolated to infinity.

DOSING STUDIES

To determine if the %T>MIC required for efficacy was similar for both ESBL and non-ESBL producing gram-negative bacilli, we studied the activity of 6-hourly dosing regimens of Doripenem against 10 strains of gram-negative bacilli with MICs varying from 0.015 to 0.50 mg/L. For the gram-negative bacilli both cephalosporin-susceptible and -resistant strains (due to ESBL production) were used.

Doripenem was administered subcutaneously. Dose levels ranged from 0.01-56 mg/kg. Each dose level was provided every 6 h (4 times) over the 24 h treatment period.

DATA ANALYSIS

Each of the dose-response curves was mathematically characterized using a maximum effect model. This methodology uses the Hill equation to estimate by non-linear regression the maximum effect (Emax), the dose (P50) required to obtain 50% of the Emax, and the slope of the dose-response relationship. From these parameters we can then calculate the dose required to produce a net bacteriostatic effect over 24 hours. These parameters were also used to calculate the dose required to produce a 1 and 2 log organism kill.

Methods, continued

HUMAN PHARMACOKINETICS AND MONTE CARLOS SIMULATION

Phase I pharmacokinetic (PK) data from a double-blind, dose escalation study of intravenous DOR in 24 healthy subjects who received 1 of 4 regimens for 7 days, 500 or 1000 mg given q12h or q8h were described by a 2-compartment model with linear elimination. Interindividual variability and the covariance between parameters were estimated for CL, Vc, and Vp and an additive plus proportional residual error model was utilized.[1]

Using mean PK parameter estimates and a covariance matrix obtained from the above-described population PK model, a 5000 patient Monte Carlo simulation (MCS) was conducted to evaluate PK-PD target attainment (based on free drug concentrations) for DOR regimens of interest (doses of 250, 500, 750, 1000, 2000, 3000 mg; intervals of q6h, q8h, q12h, q24h; infusion durations of 1-6 & 24 h).[1]

PK-PD targets were defined as the target exposure associated with a static and/or 1-log kill. Simulations based on a range of doubling MIC dilutions from 0.25-16 mg/L were considered.

Table 1. Doripenem In vitro Activity Against Cephalosporin-Susceptible and -Resistant Gram Negative Bacilli

Organism	Doripenem MIC (mg/L)	Cefepime MIC (mg/L)	Ceftazidime MIC (mg/L)	Comment
E. coli 25922	0.015	1.0	1.0	-
E. coli 145	0.03	8.0	16.0	SHV2
E. coli 154	0.06	8.0	32.0	TEM27
K. pneumoniae 43816	0.06	1.0	0.5	-
K. pneumoniae 51504	0.06	0.5	1.0	-
K. pneumoniae 149	0.06	32.0	4.0	SHV1, CTX M10
K. pneumoniae 152	0.06	8.0	1.0	CTX M9
E. cloacae 31-59a	0.25	4.0	128.0	Amp C
E. cloacae 31-54a	0.50	0.12	1.0	Amp C
P. aeruginosa 27853	0.50	0.5	0.5	-

Results

ANIMAL PHARMACOKINETICS

The elimination half-life in the mice ranged from 0.19 to 0.29 hours. The mean AUC/dose in mice was 0.28 (range 0.18-0.36). The mean peak/dose ratio was 0.59 (0.29 to 0.84).

The protein binding of Doripenem in mouse plasma, as determined by ultrafiltration, was less than 5%.

MAGNITUDE OF TIME ABOVE MIC NECESSARY FOR EFFICACY

The static doses varied from 6.15 mg/kg every 6 hrs to 55.6 mg/kg every 6 hrs. The time above MIC values associated with these static doses varied from 20 to 38%. The static doses, 1 and 2 log kill doses for each of the drug-organism combinations and the various dosing regimens are shown in Table 2. The extent of bacterial killing was relatively similar for most strains.

Extended-spectrum beta-lactamase production in gram-negative bacilli also did not impact the magnitude of the time above MIC necessary for efficacy.

The relationships between doripenem time above MIC and efficacy against the organisms is shown in Figure 2. The relationship among the data for each of the 10 strains studied was strong as demonstrated by the R^2 value (0.69).

HUMAN PHARMACOKINETICS AND MONTE CARLO SIMULATION

Table 3 demonstrates the impact of varying dose, interval, and infusion durations on PK-PD target attainment (%) at MICs of 0.12 and 0.25 mg/L.

Figures 3, 4 and 5 demonstrate the plasma concentration-time profiles for different durations of infusion for a 125, 250, and 500 mg dose, respectively. Within each plot, the MIC distributions for ESBL-producing K. pneumoniae and E. coli are also displayed.

Table 2. Doripenem In vivo Activity in a Murine Thigh Infection Model Against Gram-Negative Bacilli

Organism	MIC (mg/L)	SD (mg/kg)	%T>MIC	1 Log (mg/kg)	%T>MIC	2 Log (mg/kg)	%T>MIC
E. coli 25922	0.015	22.1	38	113	47	na	na
E. coli 145	0.03	6.15	33	12.4	35	253	51
E. coli 154	0.06	7.32	28	24.7	30	97.4	38
K. pneumoniae 43816	0.06	29	29	75.3	35	210	46
K. pneumoniae 51504	0.06	55.6	34	216	49	na	na
K. pneumoniae 149	0.06	26.3	28	56.4	34	116	40
K. pneumoniae 152	0.06	12.6	31	98	39	1111	54
E. cloacae 31-59a	0.25	38.3	26	158	37	1074	47
E. cloacae 31-54a	0.50	23.7	20	78.4	27	276	36
P. aeruginosa 27853	0.50	46	23	100	28	245	35
mean ± SD			29 ± 5.3		36.1 ± 7.4		43.3 ± 7.1

Conclusions

1] The magnitude of the %T>MIC required for a static effect with Doripenem was similar to that previously observed with other carbapenems.

2] Drug resistance due to ESBL production did not impact the %T>MIC required for efficacy.

3] These data suggest that Doripenem may be useful for the treatment of infections caused by ESBL-producing bacteria

Outcomes

Table 3. Comparison of PK-PD Target Attainment by Dosing Regimen, MIC, and Duration of Infusion

Dosing Regimen	MIC	Duration of Infusion (hrs)	Percent of Patients Achieving T>MIC Target			
			35%T>MIC	40%T>MIC	45%T>MIC	50%T>MIC
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500 mg q12h	0.12	1/2/3	100/100/100	100/100/100	100/100/100	100/100/100
125 mg q12h	0.25	1/2/3	70/99/100	9/69/100	0/8/74	0/0/10
250 mg q12h	0.25	1/2/3	100/100/100	94/100/100	41/94/100	3/39/95
500 mg q12h	0.25	1/2/3	100/100/100	100/100/100	99/100/100	76/99/100
250 mg q8h	0.25	1/2/3	100/100/100	100/100/100	100/100/100	100/100/100
125 mg q24h	0.25	24	98	98	98	98

Figure 1

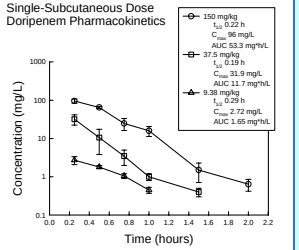

Figure 2

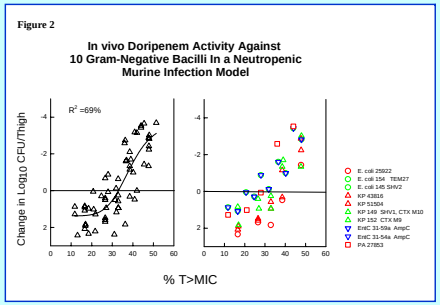

Figure 3 Simulated Concentration-Time Profiles for a 125 mg Dose

Profiles Based on Average Subject

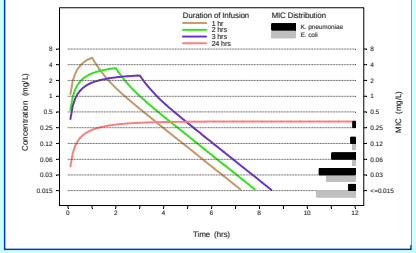

Figure 4 Simulated Concentration-Time Profiles for a 250 mg Dose

Profiles Based on Average Subject

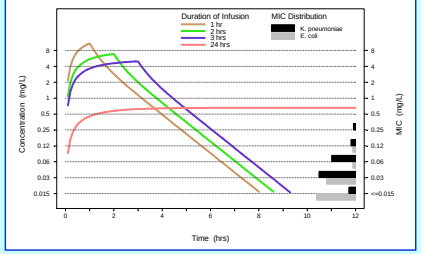

Figure 5 Simulated Concentration-Time Profiles for a 500 mg Dose

Profiles Based on Average Subject