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Pharmacodynamic Evaluation of Extending the Administration Time of Meropenem using a Monte Carlo Simulation

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A Monte Carlo simulation demonstrated that 1 g of meropenem (MEM) every 8 h (q8h) (3-h infusion) has a higher target attainment rate against *Pseudomonas aeruginosa* than either 500 mg of MEM q8h (3-h infusion) or 0.5 g of imipenem-cilastatin (I-C) q6h (1-h infusion). For other pathogens, 500 mg of MEM q8h was equivalent or superior to I-C.

For β-lactams, the optimal pharmacodynamic parameter predicting microbiologic efficacy is the time the concentration in serum remains above the MIC (T>MIC) (12). For carbapenems, a regimen which provides a T>MIC of 40% of the dosing interval appears sufficient to cause near-maximal microbial kill (2, 7). Simulations were performed to determine meropenem regimens which would be equivalent to or exceed predicted microbial eradication success rates with 500 mg of imipenem every 6 h.

Serum meropenem pharmacokinetic (PK) data were obtained from Astra-Zeneca. These data contain 2,203 plasma meropenem concentration measurements from 18 studies involving 110 volunteers and 46 patients. Samples were taken between 5 min and 12 h after a single (or first) dose of 250 to 2,000 mg was given as an infusion over 5 to 30 min. Imipenem PK data were obtained from previously published data from six healthy volunteers (5). MIC distribution curves for organisms likely to be seen as a cause of nosocomial infection were obtained from the global Meropenem Yearly Susceptibility Testing Information Collection (MYSTIC) database for the period 1997 through spring 2002. This database may be biased to larger institutions with relatively high rates of microbial resistance.

The apparent volume of the central compartment, the intercompartmental transfer rate constants (K_{cp} and K_{pc}), and the plasma clearance were identified by a population PK analysis (nonparametric adaptive grid for imipenem and nonparametric expectation maximization for meropenem). Weighting assumed that the true observation variance was proportional to the assay variance.

The population mean parameter vector and full covariance matrix from each analysis was inserted into Subroutine Prior of the ADAPT II package of programs of D'Argenio and Schumitzky (3). They were used for the generation of 2,500-subject Monte Carlo (MC) simulations for a two-compartment open model with zero-order infusion (1.0 or 3.0 h) and first-order elimination and transfer rate constants. The MC simulation was performed to estimate the probability of attaining a target meropenem or imipenem T>MIC of 40% (maximum cell kill) with each regimen, with MICs ranging from 0.25 to 16.0 mg/liter. A log normal distribution was chosen because it best recaptured the initial parameter values and their dispersions. SYSTAT for Windows version 10.0 was used for all data transformation.

This model was used to determine the probability of 500 mg of meropenem every 8 h or 1 g of meropenem every 8 h (each as a 3-h infusion) or 500 mg of imipenem every 6 h as a 1-h infusion achieving a T>MIC of 40%.

Overall population target attainment rates were determined by taking an expectation over the product of the fraction of the isolates at a specific MIC and the target attainment rate at that MIC.

The MICs at which 50 and 90% of the isolates tested are inhibited (MIC_{50}s and MIC_{90}s, respectively) and the number of isolates tested for the organisms of interest are presented in Table 1. The MIC distributions of imipenem and meropenem used in the MC analysis are listed in Table 2. The mean parameter vector and covariance matrix population pharmacokinetic modeling values are reported in Table 3 for imipenem and meropenem.

The target attainment rate against 6,500 strains of *Pseudomonas aeruginosa* for 1 g of meropenem every 8 h was superior to either 500 mg of meropenem every 8 h or 500 mg of imipenem every 6 h. The target attainment rate of 500 mg of meropenem every 8 h was >98% for methicillin-susceptible *Staphylococcus aureus*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., and *Proteus* spp. The overall population percent target attainment by pathogen for each of the three regimens tested is summarized in Table 4. Finally, further analysis of four different meropenem regimens in comparison to the distribution curve of *P. aeruginosa* was undertaken (Table 5). As demonstrated in Table 4, with the exceptions of *P. aeruginosa* and *Acinetobacter* species, several dosing regimens provided adequate coverage of the organisms tested. Table 5 compares other meropenem regimens against *P. aeruginosa*.

One gram of meropenem administered over 30 min in humans produces a peak concentration in serum of approximately 50 to 60 mg/liter in healthy volunteers with normal renal function, but after 8 h the serum concentration is 0.25 mg/liter (6). Because meropenem (like imipenem) has a very short half-life, either frequent administration or continuous infusion has been used to maintain adequate T>MIC.

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TABLE 1. MIC_{50}s and MIC_{90}s from the MYSTIC database, 1997 to spring 2002

Organism(s)	No. of isolates	Meropenem		Imipenem-cilastatin	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
S. aureus	5,937	≤0.25	≤0.25	≤0.25	≤0.25
Klebsiella spp.	3,884	≤0.25	≤0.25	≤0.25	0.5
Enterobacter spp.	4,005	≤0.25	≤0.25	0.5	1.0
Serratia spp.	1,145	≤0.25	≤0.25	0.5	1.0
Acinetobacter spp.	1,748	1.0	32.0	1.0	16.0
P. aeruginosa	6,500	1.0	16.0	2.0	16.0

In vitro analysis of a bolus dose versus continuous dosing of meropenem against an isolate of *S. aureus* for which the MIC was 0.063 mg/liter has demonstrated equally efficient modes of action (8). However, the MIC of the drug for this organism was so low that the concentration of free drug was always above the MIC regardless of administration method. Keil and Wiedemann (9) found the antimicrobial effects of continuous infusion of 1 g every 24 h to be superior to intermittent infusion of 3 g every 24 h against a *P. aeruginosa* isolate for which the MIC was 0.25 mg/liter. The important issue in these studies is the MIC for the test strain. Obviously, the higher the MIC, the harder it is to maintain 40% T>MIC. The advantages of continuous infusion (or prolonged infusion, for that matter) are greatest when an organism for which the MIC is high is being treated.

The pharmacokinetics of continuous meropenem administration in humans have been reported by Thalhammer et al. (11) and Sorgel et al. (10). The former have also published a successful case in which a 2-g meropenem load was followed by a continuous infusion of 8 g per day (new solution prepared every 6 h) in a critically ill patient with multidrug-resistant *P. aeruginosa* for which the meropenem MIC was 32 mg/liter (4). In healthy volunteers, 1.5 or 3 g per day as a continuous infusion produces steady-state concentrations and standard deviations of 4.49 ± 0.71 or 7.62 ± 1.53 mg/liter, respectively (10). Others have investigated the bactericidal activity of daily administration of 1.5 or 3.0 g of meropenem via continuous infusion and found that clinically relevant rates of killing are achieved for strains for which the MICs are up to 2 mg/liter (1.5 g/day) or 4 mg/liter (3.0 g/day) (1).

TABLE 3. Population PK modeling for imipenem and meropenem: mean parameter vector and covariance matrix

Drug and value	Vc (liter)	K_{cp} (h^{-1})	K_{pc} (h^{-1})	CI (liter/h)
Imipenem				
Mean	14.48	0.26	0.79	13.38
Covariance matrix	6.26			
	−0.29	0.17		
	−1.13	0.70	0.30	
	−1.13	−0.58	0.76	1.42
Meropenem				
Mean	13.38	2.42	9.73	13.57
Covariance matrix	12.52			
	−0.61	14.21		
	24.29	31.77	134.28	
	2.67	0.89	5.29	1.13

Continuous infusion ties up a line for the entire day. Given issues with drug incompatibility, this will drive placement of other lines, particularly in critically ill patients. Extra lines are associated with a higher probability of a line infection, which is associated with higher morbidity and cost. Prolonged infusion obviates this problem. In addition, it maximizes the target attainment rate, because the duration of the infusion approximates the duration of coverage of the dosing interval with free drug in excess of the MIC that provides maximal microbiological effect.

In this analysis, it is clear that 500 mg of meropenem administered every 8 h as a 3-h infusion provides excellent coverage for the most common pathogens seen in the nosocomial environment, excluding nonfermenters (Table 4). It should be noted that the target attainment rates for this regimen meet or exceed that seen with 500 mg of imipenem-cilastatin adminis-

TABLE 2. MIC distributions for meropenem and imipenem

Drug and MIC	% of strains inhibited					
	S. aureus	*Klebsiella* spp.	*Enterobacter* spp.	*Serratia* spp.	*Acinetobacter* spp.	*P. aeruginosa*
Meropenem						
0.25	92.08	93.98	92.1	90.83	21.35	28.53
0.5	3.12	1.83	3.64	3.76	18.6	16.61
1.0	1.6	2.55	2.2	3.58	18.15	14.69
2.0	1.18	1.03	1.21	0.96	12.71	12.18
4.0	0.47	0.13	0.39	0.35	6.87	7.95
8.0	0.34	0.1	0.26	0.09	6.12	7.29
16.0	0.27	0.08	0.03	0.09	3.66	4.72
32.0	0.89	0.13	0.03	0	6.53	4.06
Imipenem						
0.25	90.8	71.52	46.35	27.77	30.03	4.85
0.5	3.57	15.04	25.4	31.18	14.53	7.4
1.0	1.4	6.69	14.5	22.53	13.9	18.89
2.0	2.32	2.32	9.46	12.4	12.59	23.11
4.0	0.45	0.45	2.62	4.1	5.55	15.48
8.0	0.22	0.22	0.95	0.96	4.35	8.98
16.0	0.13	0.13	0.43	0.26	4.52	7.46
32.0	0.98	0.28	0.07	0.26	8.24	7.03

TABLE 4. Percent target attainment (T>MIC 40%)

Organism(s)	Imipenem, 500 mg q6h (1-h infusion)	Meropenem, 500 mg q8h (3-h infusion)	Meropenem, 1 g q8h (3-h infusion)
S. aureus	98.5	98.4	98.8
Klebsiella spp.	99.0	99.5	99.6
Enterobacter spp.	98.0	99.5	99.8
Serratia spp.	97.5	99.4	99.6
Acinetobacter spp.	76.0	77.1	83.0
P. aeruginosa	73.0	79.3	86.4

tered as a 1-h infusion every 6 h. A prolonged infusion (2.4-h infusion) simulation was not performed for this agent because of stability issues addressed in the product package insert.

For *P. aeruginosa* and *Acinetobacter* species, the larger dose (1.0 g q8h) as a 3-h infusion provided higher target attainment rates. It should be noted that no statistical testing was performed for these differences in rates because these are simulated data. Any differences could be driven to significance merely by increasing the size of the simulation. The point estimates of the target attainment rates provide guidance, however, for attaining a specific target (T>MIC associated with near-maximal microbiological effect). The use of prolonged infusions provides a method for improving microbiological coverage with virtually no cost, and by not giving the infusion continuously, the practical difficulties associated with this form of administration are surmounted. This method can be employed for other stable drugs of the β-lactam class where the prolonged infusion time does not cause undue drug degradation (e.g., piperacillin-tazobactam).

TABLE 5. Meropenem target attainment against *P. aeruginosa* using four different dosing regimens

MIC	% of isolates inhibited by:				
	1 g q8h (3 h)[a]	1 g q8h (1 h)	500 mg q8h (3 h)	500 mg q8h (1 h)	500 mg q6h (1 h)
0.008	100	100	100	99.95	100
0.016	100	100	100	99.8	100
0.125	100	99.99	100	99.45	100
0.25	100	99.97	100	98.65	99.84
0.5	100	99.82	100	95.4	99.36
1.0	100	99.28	100	89.65	97.04
2.0	100	96.21	99.25	65.45	88.04
4.0	99.1	81.08	79.6	31.9	63.02
8.0	79.6	23.12	14.2	4.4	19.08
16.0	14.2	0	0	0	0
32.0	0	0	0	0	0
Target attainment	86.4	79.5	79.3	67.5	76.4

[a] Values in parentheses are infusion times.

Based on this simulation, we predict that 500 mg of meropenem administered every 8 h as a 3-h infusion is at least comparable in the probability of attaining maximal cell kill to the more traditional dosing of 1.0 g administered every 8 h as a 30-min infusion for all tested pathogens, with the exceptions of *P. aeruginosa* and *Acinetobacter baumannii*. For these two pathogens, a regimen of 1.0 g administered every 8 h, infused over 3 h, would provide near-optimal pharmacodynamics. The ultimate utility of our proposed regimens needs to be confirmed by controlled clinical trial.

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