PHARMACODYNAMIC-BASED DOSAGE REGIMENS FOR IMIPENEM, MEROPENEM AND DORIPENEM TO TREAT MELIOIDOSIS: A MONTE CARLO SIMULATION

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Abstract. Melioidosis, caused by *Burkholderia pseudomallei* (BP), is treated with ceftazidime or carbapenems. We aimed to determine the optimal pharmacodynamic-based dosage regimens and infusion times for imipenem (IMP), meropenem (MER) and doripenem (DOR) to treat melioidosis in order to inform treatment protocols for melioidosis. For this study, we used the Monte Carlo simulation to determine both conventional and prolonged infusion regimens for IMP , MER and DOR involving 10,000 simulated patients based on the likelihood of achieving free drug concentrations above the minimum inhibitory concentration (MIC; $fT > MIC$) of the studied drugs for this organism, the probability of attaining (PTA) a $fT>MIC$ and the cumulative fraction of response (CFR) of the studied organism to the studied antimicrobials, which was calculated as the proportion of %PTA of T>MIC for each MIC according to the MIC distribution. The optimal pharmacokinetic-pharmacodynamic (PK/PD) target for this study was 40% of the $fT>MIC$. This percentage correlates with the *in vivo* efficacy for carbapenems. The pharmacokinetic parameters for the studies carbapenems were obtained from the published literature. The minimum inhibitory concentrations (MICs) for IMP, MER and DOR used for this study were derived from 100 BP clinical isolates obtained from hospitalized patients at Siriraj Hospital, Thailand. The MICs to inhibit 50% of each isolate (MIC_{50}) for IMP, MER and DOR were 0.5 μg/ml, 1 μg/ml and 1.5 μg/ml. MICs to inhibit 90% of each isolate (MIC_{90}) for IMP, MER and DOR were 0.75 μg/ml, 1.5 μg/ml and 3 μg/ml. Susceptibilities were determined according to the Clinical and Laboratory Standards Institute (CLSI). The percentage of the isolates susceptible to IMP, MER and DOR were 96%, 96% and 85%, respectively. IMP at a regimen of 0.5 g every 6 hours (0.5 hour infusion time), 0.5 g every 8 hours 0.5 g every 6 hours and 1 g every 8 hours (3 hour infusion time). all achieved CFR 90%. All MER regimens achieved on optimal CFR (98.21-100%). The DOR regimens to achieved >90% CFR were 0.5 g, 1 g and 2 g every 8 hours (4 hour infusion time). Our results show the best carbapenem drug regimens to treat melioidosis. *In vivo* studies are needed to determine if these regimens improve outcome compared to currently used regimens to treat melioidosis in the study population.

Keywords: melioidosis, imipenem, meropenem, doripenem, pharmacokinetics / pharmacodynamics, Monte Carlo simulation

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INTRODUCTION

Melioidosis, is caused by an infection with the gram-negative bacterium *Burkholderia pseudomallei* (BP) and is endemic in Southeast Asia and northern Australia (Wiersinga *et al*, 2012). The disease is associated with high morbidity (12.7 cases of melioidosis per 100,000 people per year) and mortality (42.6%) in northeastern Thailand (Curries *et al*, 2010; Limmathurotsakul *et al*, 2010). Melioidosis is usually treated with 10-14 days of intravenous ceftazidime or meropenem (Cheng, 2010; Dance, 2014) along with eradication therapy using trimethoprim-sulfamethoxazole for 3-6 months (Cheng, 2010). Appropriate treatment can reduce mortality and eradication therapy can reduce recurrent infections (Dance, 2014).

However, ceftazidime-resistant *B. pseudomallei* has been reported in the literature (Kung *et al*, 2010; Sarovich *et al*, 2012). The possible mechanisms for ceftazidime resistance include loss of penicillin-binding protein 3 (PBP3) (Chantratita *et al*, 2011), the presence of an efflux pump (Sirijant *et al*, 2016) and mutation of the *PenA* β-lactamase gene (Kung *et al*, 2010). A case report of a Thai patient with ceftazidime resistant found a P167S mutation, making the bacteria resistant to ceftazidime but sensitive to amoxicillin/clavulanate, imipenem and meropenem (Sarovich *et al*, 2012). Identifying the appropriate antibiotic regimen is essential to reducing mortality and morbidity among the patients with ceftazidime-resistant BP.

Carbapenems have some benefits over ceftazidime in being more rapidly bactericidal (Smith *et al*, 1994) and having a longer post-antibiotic effect with less endotoxin release (Walsh *et al*, 1995). The minimum inhibitory concentration to inhibit 90% of the growth of each isolate (MIC_{90}) of BP to doripenem (1.5 μg/ml) is similar to meropenem (1.5 μg/ml) (Thamlikitkul and Trakulsomboon, 2009; Harris *et al*, 2011) and may be effective for treating melioidosis.

The Monte Carlo simulation (MCS), a pharmacokinetic/pharmacodynamic (PK/PD) method, is commonly used to evaluate antibacterial dosing regimens (Trang *et al*, 2017). Several studies found that using the PK/PD properties of carbapenems by giving a prolonged or continuous infusion was associated with clinical success for treating several multidrug resistant gram-negative infections (Falagas *et al*, 2013; Crandon *et al*, 2016). Patients receiving a prolonged infusion (≥3 hour intravenous infusion) or continuous infusion (24 hour intravenous infusion) of a carbapenem or piperacillin/tazobactam had lower mortality rates than patients who received conventional regimens (20-60 minute intravenous infusion times) (Falagas *et al*, 2013). A study evaluating the treatment of ventilator-associated pneumonia due to *Pseudomonas aeruginosa* found a significant relationship between the carbapenem pharmacodynamic and the outcome and survival (Crandon *et al*, 2016).

In this study, we aimed to determine the optimal pharmacodynamic-based dosage regimens and infusion times for imipenem, meropenem and doripenem to treat melioidosis by using Monte Carlo simulation.

MATERIALS AND METHODS

Microbiology

One hundred isolates of *B. pseudomallei* were obtained from 100 subjects with melioidosis presenting to Siriraj hospital, Bangkok, Thailand during January-December 2010. The number of isolates in this study was small due to small numbers of *B. pseudomallei* infected patients at the study hospital. A sample size $\geq$ 50 was considered adequate to provide robust and realistic pharmacokinetic predictions for this study (Tam *et al*, 2006). Patient specimens were collected and confirmed by the laboratory to be the study species. The minimum inhibitory concentrations (MICs) to inhibit 50% of the growth of each isolate (MIC_{50}) and the MICs to inhibit 90% of the growth of each isolate (MIC_{90}) of imipenem, meropenem and doripenem was determined following the Clinical and Laboratory Standards Institute guidelines (CLSI, 2016). Susceptibilities were also determined according to CLSI guideline (CLSI, 2016). CLSI breakpoints [MICs that define microorganisms as susceptible, intermediate or resistant to antibiotics (de Velde *et al*, 2018)] for *P. aeruginosa* (<2 μg/ml) were applied (CLSI, 2016). This study protocol was approved by Siriraj Ethics Committee, Faculty of Medicine Siriraj Hospital, Mahidol University. (Ethics Committee approval number: 008/2551).

Antimicrobials

Conventional regimens (0.5 hour or 1 hour infusion time) and prolonged infusion regimens (3 hour or 4 hour infusion time) of imipenem, meropenem and doripenem were simulated as follows: imipenem 0.5 g every 8 hours (0.5 hour infusion time), imipenem 0.5 g every 6 hours (0.5 hour infusion time), imipenem 1 g every 8 hours (0.5 hour infusion time), imipenem 0.5 g every 8 hours (3 hour infusion time), imipenem 0.5 g every 6 hours (3 hour infusion time), imipenem 1 g every 8 hours (3 hour infusion time), meropenem 0.5 g every 8 hours (0.5 hour infusion time), meropenem 0.5 g every 6 hours (0.5 hour infusion time), meropenem 1 g every 8 hours (0.5 hour infusion time), meropenem 2 g every 8 hours (0.5 hour infusion time), meropenem 0.5 g every 8 hours (3 hour infusion time), meropenem 1 g every 8 hours (3 hour infusion time), meropenem 2 g every 8 hours (3 hour infusion time), doripenem 0.5 g every 8 hours (1 hour infusion time), doripenem 1 g every 8 hours (1 hour infusion time), doripenem 2 g every 8 hours (1 hour infusion time), doripenem 0.5 g every 8 hours (4 hour infusion time), doripenem 1 g every 8 hours (4 hour infusion time), doripenem 2 g every 8 hours (4 hour infusion time). The pharmacodynamic exposure was measured by percentage of the free drug concentrations above the minimum inhibitory concentration (%fT > MIC) for each regimen for this study the optimum PK/PD target was set at 40% fT>MIC (Deryke *et al*, 2006).

Pharmacokinetic model

Published population pharmacokinetic data from critically ill patients with normal renal function (Sakka *et al*, 2007; Ikawa *et al*, 2009) and abnormal renal function (Crandon *et al*, 2011) were used. We used pharmacokinetic data from critically ill patients because patient with melioidosis are more likely to be critically ill. The concentration-time data for the carbapenem regimens were simulated using the two compartment model: the central compartment (plasma) and the peripheral compartment (tissue) (Ikawa *et al*, 2009) (Table 1).

Monte Carlo simulation

The Monte Carlo simulation (MCS)

Table 1
Pharmacokinetic parameters used for the Monte Carlo simulation.

Drug	Pharmacokinetic parameters mean (±SD)				
	CL_T (L/h)	V_c	k_{12} (h^{-1})	k_{21}(h^{-1})	Fu, range
Imipenem	12.3±4.2	12.2±9.93 L	7.69±5.94	8.77±8.92	0.8
Meropenem	13.96±8.91	0.210±0.115 L/kg	0.503±0.223	0.580±0.332	0.98
Doripenem	14.5±23.6	8.29±0.854 L	1.34±1.02	1.05±1.08	0.85

CL_T, total body clearance, V_c = volume of distribution of the central compartment; k_{12}, microtransfer rate constant from central to peripheral compartment; k_{21}, microtransfer rate constant from peripheral to central compartment, fu, fraction of unbound drug; SD, standard deviation (Sakka *et al*, 2007; Ikawa *et al*, 2009; Crandon *et al*, 2011).

Table 2
MIC_{50} and MIC_{90} and antimicrobial susceptibility of imipenem, meropenem and doripenem against *B. pseudomallei.*

Drug	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Susceptibility (%)
Imipenem	0.25-6	0.5	0.75	96
Meropenem	0.25-6	1	1.5	96
Doripenem	1-8	1.5	3	85

MIC, minimum inhibitory concentration; MIC_{50}, MICs to inhibit 50% of each isolate; MIC_{90}, MICs to inhibit 90% of each isolate.

(Crystal Ball 2010 V.2.2; Decisioneering, Denver, CO) was used to simulate 10,000 patients treated for all studied carbapenem regimens to estimate the concentration-time data. We calculated the likelihood of achieving a *f*T > MIC, probability of attaining (PTA) 40% of *f*T>MIC and cumulative fraction of response (CFR) for each regimen. CFR was calculated as the proportion of % PTA the MIC based on the MIC distribution. A dosage regimen was considered optimal if the CFR was > 90%.

RESULTS

The MIC_{50} and MIC_{90} for *B. pseudomallei* imipenem, meropenem and doripenem and the percent susceptibilities to imipenem, meropenem and doripenem are shown in Table 2. MIC_{50} and MIC_{90} to imipenem, meropenem and doripenem were 0.5 and 0.75 μg/ml and 1 and 1.5 μg/ml and 1.5 and 3 μg/ml, respectively. Susceptibility rates to imipenem, meropenem and doripenem were 96%, 96% and 85%, respectively.

CFR of the carbapenem regimens against *B. pseudomallei* are shown in Table 3. Imipenem 0.5 g every 8 hours (0.5 hour infusion time) achieved CFR 83.62%, imipenem 0.5 g every 6 hours (0.5 hour infusion time) achieved CFR 91.51%, imipenem 1 g every 8 hours (0.5 hour infusion time) achieved CFR 89.29%, imipenem 0.5 g every 8 hours (3 hour infusion time) achieved CFR 97.85%, imipenem 0.5 g every 6 hours (3 hour infusion time) achieved CFR 98.76%, imipenem 1 g

every 8 hours (3 hour infusion time) achieved CFR 99.65%. Meropenem 0.5 g every 8 hours (0.5 hour infusion time) achieved CFR 98.21%, meropenem 0.5 g every 6 hours (0.5 hour infusion time) achieved CFR 99.16%, meropenem 1 g every 8 hours (0.5 hour infusion time) achieved CFR 99.73%, meropenem 2 g every 8 hours (0.5 hour infusion time) achieved CFR 99.99%, meropenem 0.5 g every 8 hours (3 hour infusion time) achieved CFR 99.30%, meropenem 1 g every 8 hours (3 hour infusion time) achieved CFR 100%, meropenem 2 g every 8 hours (3 hour infusion time) achieved CFR 100%. Doripenem 0.5 g every 8 hours (1 hour infusion time) achieved CFR 70.47%, doripenem 1 g every 8 hours (1 hour infusion time) achieved CFR 80.05%, doripenem 2 g every 8 hours (1 hour infusion time) achieved CFR 87.13%, doripenem 0.5 g every 8 hours (4 hour infusion time) achieved CFR 93.75%, doripenem 1 g every 8 hours (4 hour infusion time) achieved CFR 98.57%, doripenem 2 g every 8 hours (4 hour infusion time) achieved CFR 99.70%.

Table 3
Comparison of cumulative fraction of response (CFR) for antimicrobial treatment regimens against *B. pseudomallei*

Antibiotic regimens (infusion duration)	CFR (%)
Imipenem	
0.5 g q8h (0.5h)	83.62
0.5 g q6h (0.5h)	91.51
1 g q8h (0.5h)	89.29
0.5 g q8h (3h)	97.85
0.5 g q6h (3h)	98.76
1 g q8h (3h)	99.65
Meropenem	
0.5 g q8h (0.5h)	98.21
0.5 g q6h (0.5h)	99.16
1 g q8h (0.5h)	99.73
2 g q8h (0.5h)	99.99
0.5 g q8h (3h)	99.30
1 g q8h (3h)	100
2 g q8h (3h)	100
Doripenem	
0.5 g q8h (1h)	70.47
1 g q8h (1h)	80.05
2 g q8h (1h)	87.13
0.5 g q8h (4h)	93.75
1 g q8h (4h)	98.57
2 g q8h (4h)	99.70

q_h = every __ hours.

DISCUSSION

In this study, MIC_{90} for imipenem, meropenem and doripenem against *B. pseudomallei* were 0.75, 1.5 and 3 μg/ml, which resulted in high susceptibility rates (85-96%). CLSI breakpoints for *P. aeruginosa* (<2 μg/ml) (CLSI, 2016) were applied in our study since there were no CLSI breakpoints for imipenem, metropemem or doripenem. MIC_{90} values of imipenem was similar to a previous study in Malaysia (0.75 *vs* 0.75 μg/ml) (Sam *et al*, 2010), the data of which was collected between 1987-2007. MIC_{90} values of meropenem were similar to the study of Harris *et al* (2011) (1.5 *vs* 1.5 μg/ml) the data of which was collected in Australia in 2010. The MIC_{90} value for doripenem in our study was higher than a previous study in Thailand in 2009 (3 *vs* 0.75 μg/ml) (Thamlikitkul and Trakulsomboon, 2009). The MIC range for doripenem in our study (1-8 μg/ml) was higher than a previous study (0.19-2 μg/ml) in Thailand in 2009 (Thamlikitkul and Trakulsomboon, 2009).

The different MIC values of doripenem may be caused by the different use rate. There were several studies showing the relation between increasing carbapenem exposure and antimicrobial resistance (McLaughlin *et al*, 2013; Plüss-Suard *et al*, 2013; Mladenovic-Antic *et al*, 2016).

In our study, we simulated both conventional and prolonged infusion time drug regimens. Of these, all the conventional meropenem regimens, one of the imipenem regimen (0.5 g every 6 hours, 0.5 hour infusion time) and none of the doripenem regimens had a CFR > 90%. However, all the prolonged infusion regimens for each of the 3 studied carbapenems had a CFR >90%. There are no previous studies using the Monte Carlo simulation to evaluate carbapenem treatment of *B. pseudomallei*. Several studies have used the Monte Carlo simulation to evaluate carbapenem treated of *P. aeruginosa* (Esterly *et al*, 2010; Roberts *et al*, 2011; Crandon *et al*, 2016; Koomanachai *et al*, 2016; Suchánková *et al*, 2017). In our study, only some of the conventional regimens gave a CFRs >90% unlike previous studies using *P. aeruginosa* where none of the conventional regimens for imipenem, meropenem and doripenem had a CFRs >90% (Roberts *et al*, 2011; Koomanachai *et al*, 2016); the MIC_{90} for imipenem, meropenem and doripenem against *P. aeruginosa* in one study were high (>32, >32 and >32 μg/ml, respectively) (Koomanachai *et al*, 2016) and in another study were very high (>64, >64 and >64 μg/ml, respectively) (Roberts *et al*, 2011). In our study all the prolonged regimens gave a CFRs >90%. Our findings are different from a study by Roberts *et al* (2011) that repeated none of the prolonged infusion imipenem or meropenem regimen and only 1 doripenem regimen (1 g every 8 hours, 4 hour infusion time) resulted in a CFR > 90% and in 2 other studies (Roberts *et al*, 2011, Koomanachai *et al*, 2016) that found doripenem (2 g every 8 hours, 4 hour infusion time) gave a CFR > 90% against *P. aeruginosa*. The reason might be different MIC distribution of *B. pseudomallei* in this study.

Our study showed a prolonged infusion gave a better result than the conventional carbapenem regimen, similar to previous studies (Esterly *et al*, 2010; Falagas *et al*, 2013; Crandon *et al*, 2016; Thompson *et al*, 2016; Suchánková *et al*, 2017). A prolonged infusion of the same daily dose gave a greater chance of resulting in a CFR > 90%. The lowest dosage regimens to result in a CFR > 90% for imipenem, meropenem and doripenem were imipenem 0.5 g every 8 hours (3 hour infusion time), meropenem 0.5 g every 8 hours (3 hour infusion time) and doripenem 0.5 g every 8 hours (4 hour infusion time).

Our study had several limitations: the MICs for *B. pseudomallei* in our study were obtained from a single tertiary care referral hospital in Bangkok, Thailand and cannot be applied to other locations or institutions. Our sample size were small (only 100 isolates). The pharmacokinetic data used in our study was obtained from a non-Southeast Asia population, which may mean the results are less accurate. Normal renal function was assumed in our study simulations. Patients with renal impairment need a change in dosage regimen based on creatinine clearance.

Carbapenems are an alternative treatment for patients with melioidosis. Prolonged infusion times (3-4 hours) resulted in better pharmacodynamics exposure. Further studies are needed to determine if difference infusion times will result in different clinical outcomes among study patients.

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