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Optimizing intravenous fosfomycin dosing in combination with carbapenems for treatment of *Pseudomonas aeruginosa* infections in critically ill patients based on pharmacokinetic/pharmacodynamic (PK/PD) simulation

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ABSTRACT

Objective: The purpose of the study was to determine the optimal dosing regimen of intravenous fosfomycin for the treatment of *Pseudomonas aeruginosa* (PA) based on PK/PD targets.
Method: A total of 120 PA isolates were recovered from various clinical specimens at university hospital in Thailand. Minimum Inhibitory Concentrations (MICs) of all the isolates were determined by the E-test method. PK parameters were obtained from a published study. Monte Carlo simulation was performed to calculate the percentage of target attainment (PTA) and cumulative fraction of response (CFR).
Results: MIC_{90} of fosfomycin alone, fosfomycin in combination with carbapenem, carbapenems alone and carbapenems in combination with fosfomycin were >1,024, 1,024, >32 and 32 μg/ml, for multidrug resistant (MDR)-PA and 512, 128, 8 and 3 μg/ml respectively, for non-MDR PA. Approximately 40% of the non-MDR PA were carbapenem-resistant strains. For non-MDR PA with CRPA, fosfomycin 16 g continuous infusion in combination with carbapenems provided %PTA of approximately 80 and %CFR of > 88. While, %PTA and %CFR > 90 were achieved with fosfomycin 24 g/day prolonged infusion in combination with carbapenem.
Conclusions: Prolonged infusion of fosfomycin 16 - 24 g combined with extended carbapenem infusion could be used in non-MDR PA treatment with CRPA.

1. Introduction

Pseudomonas aeruginosa (PA) is a highly prevalent pathogen of nosocomial infections worldwide.[1,2] Data from developing countries indicates that *P. aeruginosa* is the most common cause of pneumonia in hospital (29%), and is the third most common cause of Intensive Care Unit (ICU)-acquired infections (17%).[2] The situation in Thailand is similar, with *P aeruginosa* being the most common pathogen of Hospital-Acquired Pneumonia (HAP) in that country.[3] More importantly, it is a common multidrug-resistant (MDR) gram-negative pathogen causing pneumonia in hospitalized patients.[3]

P. aeruginosa infections have a high rate of mortality (ranging from 10% to 70%) particularly in patients given inappropriate empirical therapy, immunocompromised patients, ICU patients and drug-resistant *P. aeruginosa* infections.[4–8] Drug-resistant *P. aeruginosa* in critically ill patients poses a treatment challenge, with the available antibiotics of choice for this pathogen, such as carbapenems, becoming gradually less effective.[8–10]

A combination of antimicrobial agents is a good option for treatment of drug-resistant *P. aeruginosa* infections in critically ill patients.[11–13] Colistin has already become a standard of treatment in patients infected with drug-resistant *P. aeruginosa.*[12,13] However, nephrotoxicity associated with colistin means this medicine should be avoided in some renal insufficiency and high risk

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patients.[11,12] Antibiotics together with a combination of fosfomycin and carbapenems appear to be a possible treatment regimen.[14] Intravenous (IV) fosfomycin is an old antibiotic agent which exerts excellent *in vitro* bactericidal activity against a wide spectrum of organisms, including *P. aeruginosa*, especially in resistant strains.[14–18] In *in vitro* studies, the combination of fosfomycin with carbapenems has also shown good synergistic effects against *P. aeruginosa* isolates.[19] Some clinical trials have reported improvements in the clinical and microbiological outcomes of fosfomycin in combination with other antibiotics, such as carbapenems, for treatment of *P. aeruginosa*.[19–24] However, the reported appropriate dosage regimen of fosfomycin varied widely.[20–24;]

Pharmacokinetic/pharmacodynamic (PK/PD) studies, especially in Monte Carlo simulations, have played roles for selecting appropriate antibiotic doses with the goal of increasing treatment efficacy and reducing the risk of selecting multidrug-resistant pathogens.[25–27] Previous studies that considered antibiotic PK/PD to optimize exposure when treating resistant bacteria included many antimicrobial agents such as colistin and piperacillin/tazobactam. These studies resulted in successful outcomes.[28–31] However, previous Monte Carlo simulation studies of PK/PD dosages did not include fosfomycin.

The purpose of this current study was to find the optimal dosage regimen of fosfomycin when used in combination with carbapenem for the treatment of non-MDR-PA and MDR-PA based on PK/PD targets in critically ill patients.

2. Materials and methods

2.1. Microbiology

P. aeruginosa isolates recovered from various clinical specimens (sputum, urine, skin and soft tissue, blood, pleural fluid) at the Faculty of Medicine at Siriraj Hospital in Bangkok, Thailand, were collected between June and September 2011. A total of 120 non-MDR and MDR isolates were obtained. Minimum inhibitory concentrations (MICs) of carbapenems (imipenem, meropenem and doripenem) and fosfomycin by E test were determined for all isolates. Isolate preparation was performed according to the Clinical and Laboratory Standards Institute (CLSI 2011) protocol.[32] The MDR phenotype was identified for isolates expressing resistance to at least three different antibiotic groups: beta-lactams (penicillin, cephalosporin or carbapenems (except monobactam e.g. aztreonam), aminoglycosides and fluoroquinolones.[33] Synergy studies were conducted using an E test of fosfomycin in combination with carbapenems. E test strips of each drug used in the combination were applied in cross direction to each other and the MIC values of each drug were measured after combination.[34,35]

2.2. Pharmacodynamic Model

Pharmacodynamic exposure was measured by percentage of time above the MIC (%T > MIC) of each drug.[18,36–40] Simulations were conducted for IV infusions of the various agents and regimens: fosfomycin 1- 8 g given every 6 - 12 hours, infused over 30 minutes - 24 hours, meropenem 0.5 – 2.0 g given every 6 - 8 hours, infused over 30 minutes - 3 hours, imipenem 0.5 - 1.0 g given every 6 - 8 hours, infused over 30 minutes - 3 hours, and doripenem 0.5-2.0 given every 8 hours, infused over 30 minutes - 4 hours. PK/PD targets were defined as 70% T>MIC for fosfomycin. This breakpoint (70% T>MIC) applies when effective dosage regimens for all cell wall-active antimicrobials require serum drug concentrations exceeding the MIC of the pathogens [18,36–40] and 40% T>MIC for the carbapenems. The value 40% T>MIC is required for near-maximal bactericidal effect of the dosing interval for *Pseudomonas aeruginosa*.[37,39,40]

2.3. Pharmacokinetic Model

Pharmacokinetic data were obtained from previously published studies of critically ill patients.[41–44] A set of parameters was randomly generated according to each mean and standard deviation of the parameters. Steady-state concentration versus time was simulated using a one-compartment model for fosfomycin[41] and a two-compartment model for carbapenems to calculate %T>MIC.[42–44]

2.4. Monte Carlo Simulation

Pharmacodynamic/pharmacokinetic analysis was conducted via a 10,000-subject Monte Carlo simulation (Crystal Ball 2010 v.2.2; Decisioneering Inc., Denver, CO) for IV dosage regimens of fosfomycin and carbapenems to calculate %T> MIC based on the linear pharmacokinetic behavior of each agent. Log-normal distributions were evaluated for between-patient variability. The probability of target attainment (PTA) was calculated as the percentage of all 10,000 estimates that had a probability of attaining 40% T>MIC for carbarpenems and 70% T>MIC for fosfomycin, either used alone or in combination. The cumulative fraction of response (CFR) was calculated as the proportion of %PTA of each MIC according to the MIC distribution. The PTA and CFR $\geq$ 90% was considered optimal against a bacterial population, whereas a CFR between 80% and 90% was associated with moderate probabilities of success.[36,45]

3. Results

MDR-PA had MIC_{90} >1,024 μg/ml for fosfomycin monotherapy, 1,024 μg/ml for fosfomycin combined with carbapenems, >32 μg/ml for carbapenems monotherapy, and 32 μg/ml for carbapenems combined with fosfomycin (Table 1). While, MIC_{90} for non-MDR PA were 512 μg/ml for fosfomycin monotherapy, 128 μg/ml for fosfomycin combined with carbapenems, >32 μg/ml, 8 μg/ml and 4 μg/ml for imipenem, meropenem, and doripenem monotherapy, respectively. For carbapenem combination, MIC_{90} were 12 μg/ml for imipenem combined with fosfomycin, 3 μg/ml for meropenem combined with fosfomycin and 2 μg/ml for doripenem combined with fosfomycin, respectively. The doripenem combination with fosfomycin had a MICs lower than the other carbapenems (Figure 1). Approximately 40% of non-MDR-PA was carbapenem-resistant PA (CRPA).

A combination of fosfomycin and carbapenems decreases the MIC of CRPA. Doripenem alone has an MIC_{90} of 6 mg/ml, and fosfomycin alone has an MIC_{90} of 1024 μg/ml, whereas the combination of fosfomycin with doripenem decreases the MIC_{90} of doripenem to 2 μg/ml and fosfomycin to 128 μg/ml.(Table 1).

3.1. %PTA of fosfomycin monotherapy

Analyses of various fosfomycin regimens to test %PTA against MICs of PA for the fosfomycin monotherapy are shown in Figure 2. All fosfomycin dosage regimens achieved more than 90% PTA at MIC < 3 μg/ml. Prolonged and continuous infusions have been shown to improve PK/PD exposure compared to dosage regimens using traditional 30-minute infusions. At the susceptibility breakpoint (MIC < 32 μg/ml) from the European Committee on Antimicrobial Susceptibility Testing (EUCAST), fosfomycin 4 g every 8 hr or more dose achieved above 90% PTA. For MIC 64 μg/ml, fosfomycin 4 g every 4 hr or more dose or prolonged infusion achieved above 90% PTA. No fosfomycin monotherapy

Table 1
MICs of non-MDR PA and MDR PA isolates against tested agents, mono drugs and combination drugs.

Antimicrobial agent	Antimicrobial mono and combination drugs	Non-MDR			MDR#	
		MIC range (μg/ml)	MIC_{90} (μg/ml)	MIC_{90} Of CRPA* (μg/ml)	MIC range (μg/ml)	MIC_{90} (μg/ml)
Imipenem	monodrug	0.75 - >32	>32	>32	1.0->32	>32
	IPM + FOF	0.047 - > 32	12	12	0.38-32	32
Meropenem	monodrug	0.016 - >32	8	>32	1.0->32	>32
	MEM + FOF	0.006 - 32	3	6	0.38-32	32
Doripenem	monodrug	0.023 - >32	4	6	0.5->32	>32
	DOM + FOF	0.006 - >48	2	2	0.38-32	32
Fosfomycin	monodrug	1.5 - >1024	512	>1024	8.0 - >1024	>1024
	FOF + IPM	1.0 - 1024	128	192	8.0 - 1024	1024
	FOF + MEM	0.75 - 1024	128	192	8.0 - 1024	1024
	FOF + DOM	0.064 -1024	128	128	8.0 - 1024	1024

MDR= multidrug resistance, MICs=minimum inhibitory concentrations (μg/ml), PA=*P.aeroginosa*, CRPA= carbapenem-resistant *P.aeroginosa*, FOF = fosfomycin, DOM=doripenem, IPM=imipenem, MEM=meropenem., *= 40% of CRPA in non-MDR isolates, The susceptibility breakpoint MIC for carbapenems is less than 2 ug/ml. #

regimens were able to achieve PK/PD targets for MIC_{90} 512 and >1024 μg/ml for non-MDR-PA and MDR-PA, respectively.

3.2. %PTA of fosfomycin combination with carbapenem

The %PTA in each combination of fosfomycin and carbapenem which achieved more than 70% T>MIC_{90} and 40% T>MIC_{90}, respectively, for non-MDR PA, are summarized in Table 2. For MDR-PA, all fosfomycin combinations, with carbapenems, could not achieve the PK/PD targets. For non-MDR PA, fosfomycin 16 g continuous infusion combined with meropenem 1- 2 g, 3-hour infusion every 8 hours and doripenem 1 g, 4-hour infusion every 8 hours achieved approximately 80% for MIC_{90} 128 μg/ml of fosfomycin, 3 μg/ml for meropenem and 2 μg/ml doripenem (Table 2). The highest dose of fosfomycin, 8 g every 8 hours infusion over 6 hours in combination with high-dose meropenem or doripenem prolonged infusion can achieve better than 95% PTA. Imipenem combined with fosfomycin achieved the PK/PD target at MIC_{90} of non-MDR PA of less than 70%.

Considering the CRPA subgroup, fosfomycin 16 g continuous infusion combined with doripenem 1 g, 4-hour infusion every 8 hours achieved approximately 80% of PTA for MIC_{90} (128 μg/ml of fosfomycin, 2 μg/ml of doripenem) and combined with meropenem 2 g, 3-hour infusion every 8 hours, or Imipenem higher dose prolonged infusion, achieved the PK/PD target at MIC_{90} of CRPA less than 50% PTA. The highest dose of fosfomycin, 8 g every 8 hours infusion over 6 hours in combination with doripenem prolonged infusion, can achieve better than 95% PTA. High-dose meropenem prolonged infusion in combination with the highest dose of fosfomycin, 8 g every 8 hours infusion over 6 hours, achieved better than 65% PTA at MIC_{90} of CRPA (192 μg/ml of fosfomycin, 6 μg/ml of meropenem). For PTA of more than 90% of meropenem in combination with fosfomycin, the dosage should be fosfomycin, 8 g every 8 hours infusion over 6 hours in combination with meropenem 2 g every 8 hr prolonged infusion at MIC_{90} less than 128 μg/ml of fosfomycin and less than 6 μg/ml for meropenem. All Imipenem regimen combinations with the highest dose of fosfomycin, 8 g every 8 hours infusion over 6 hours achieved less than 50% PTA at MIC_{90} of CRPA combination.

3.3. %CFR of fosfomycin combination with carbapenem

For non-MDR PA, fosfomycin 16 g continuous infusion combined with prolonged infusion of meropenem (1-2 g infusion over

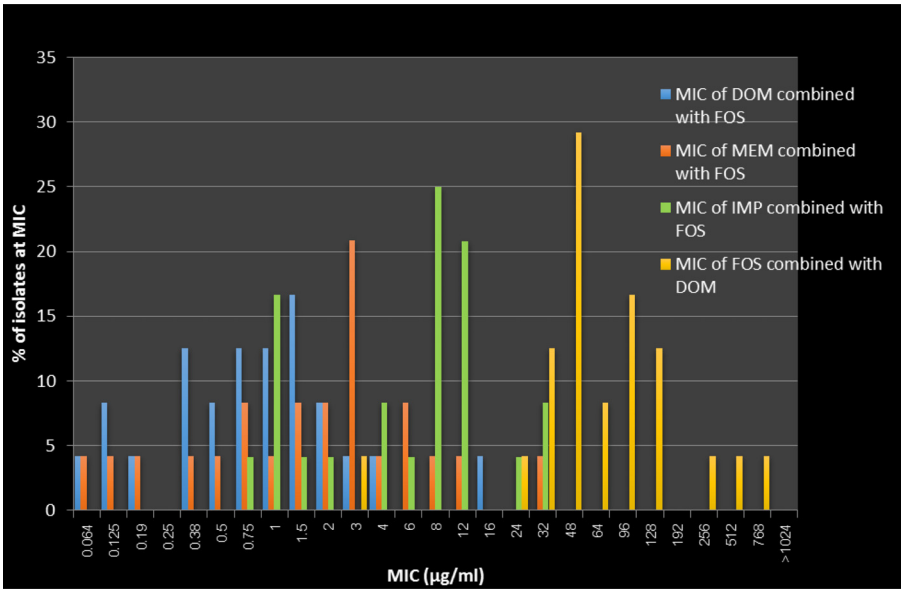

Figure 1. Minimum inhibitory concentrations (MICs) distribution of drugs in combination for carbapenem-resistant *P.aeroginosa* (CRPA), FOF = fosfomycin, DOM=doripenem, IPM=imipenem, MEM=meropenem, doripenem combination with fosfomycin had MICs lower than the other carbapenems. MIC_{90} of fosfomycin in CRPA was 128 μg/ml and MIC_{50} was 48 μg/ml.

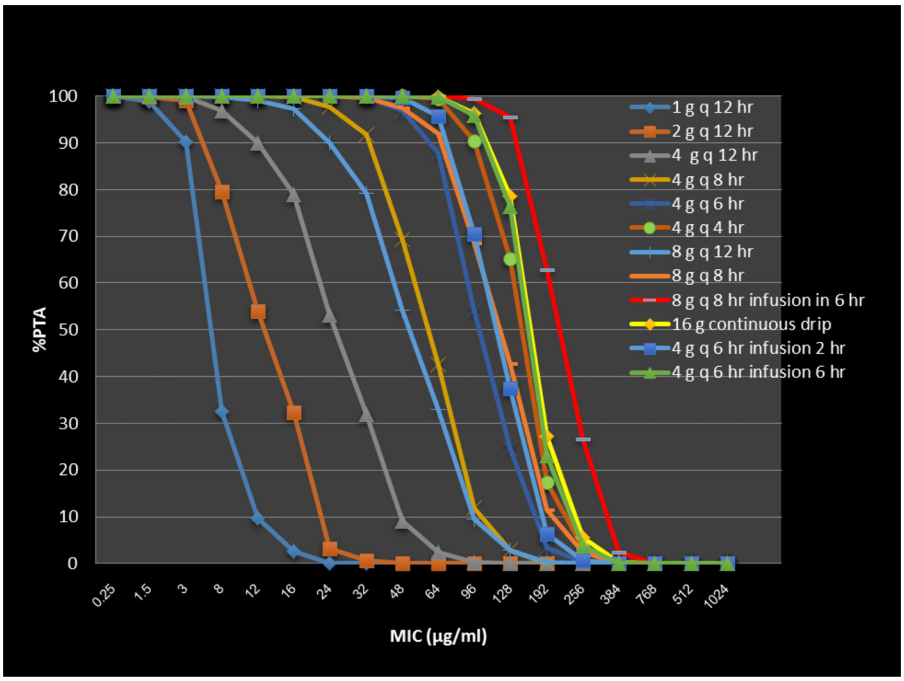

Figure 2. The probability of target attainment (%PTA) of fosfomycin monotherapy achieve more than 70% time above MIC.

3 hours every 8 hours) and doripenem (1 g infusion over 4 hours every 8 hours) achieved CFR of more than 88% (Table 3). The CFR was more than 90% with fosfomycin 8 g prolonged infusion (at least 6 hours) every 8 hours combined with high-dose prolonged infusion of meropenem or doripenem. However, PK/PD targets of %CFR for MDR-PA strains were not achieved for any fosfomycin-carbapenem combinations.

For the CRPA subgroup, fosfomycin 16 g continuous infusion combined with doripenem 1 g, 4-hour infusion every 8 hours or meropenem 2 g, 3-hour infusion every 8 hours achieved approximately 80% CFR. The highest dose of fosfomycin, 8 g every 8 hours infusion over 6 hours in combination with doripenem high dose prolonged infusion can achieve approximately 90%CFR and with high-dose meropenem (2 g, 3-hour infusion every 8 hours prolonged infusion) achieve above 85%CFR. The combination of fosfomycin with imipenem achieved less than 50% CFR.

4. Discussion

P. aeruginosa infections are likely to affect critically ill patients who require intensive care and treatment with antimicrobial agents. ICUs have a high prevalence of *P. aeruginosa* and the placement of several invasive devices introduces multiple opportunities for failure of infection control, resulting in ICUs being under considerable pressure to select broad-spectrum antibiotics.[1,11,46] The PK of antimicrobial agents in critically ill patients varies especially in volume of distribution (Vd) and clearance (CL), which may affect the drug concentration at the target sites.[47] Thus, our study chose published phamacokinetic studies of critically ill patients. Knowing the PK/PD properties of the drugs used for the management of critically ill patients is essential for selecting the appropriate dosage regimens, which will finally optimize patient outcomes.[48]

Fosfomycin inhibits uridine diphosphate-N-acetylglucosamine enolpyruvyl transferase, which is a key enzyme in early bacterial cell-wall synthesis steps.[49] The MICs of fosfomycin for *P. aeruginosa* in our study were within the range of 1.5 - >1024 µg/ml which were higher than the range indicated in other studies (1-512 µg/ml).[38] In our study, the MIC_{90} for non-MDR PA (512 µg/ml) and MDR-PA (>1024 µg/ml) were higher than those in other studies (128 and 512 µg/ml for non-MDR PA and MDR-PA, respectively).[14,15,38,49] However, a study in a teaching hospital in Thailand showed similar results to our study. That study reported MICs in the range 2->1024 µg/ml and MIC_{90} of > 1024 µg/ml.[50] Therefore, we make

Table 2
The maximum of %PTA for fosfomycin (FOF) achive more than 70% time above MIC_{90} and carbapenem (doripenem (DOM), imipenem (IPM), meropenem (MEM)) 40% time above MIC_{90} of non MDR-PA* when combinations.

%PTA of combinations	IPM 1 g q 8 h	IPM 1 g in 3 h q 8 h	DOM 1 g q 8 h	DOM 1 g in 4 h q 8 h	MEM 1 g q 8 h	MEM 1 g in 3 h q 8 h	MEM 2 g q 8 h	MEM 2 g in 3 h q 8 h
FOF 4 g q 12 h	0	0	0	0	0	0	0	0
FOF 8 g q 12 h	0	0	0	0	0	0	0	0
FOF 4 g q 8 h	1	2	2	3	3	3	3	3
FOF 4 g q 6 h	11	23	23	24	24	24	24	24
FOF 8 g q 8 h	30	30	49	49	49	49	50	50
FOF 16 g continuous infusion	32	33	77	80	80	80	80	80
FOF 8 g in 6 h q 8 h	34	35	93	95	95	96	96	96

* fosfomycin combined with carbapenems had MIC_{90} 12 µg/ml for imipenem combined with fosfomycin, 3 µg/ml for meropenem combined with fosfomycin and 2 µg/ml for doripenem combined with fosfomycin and 128 µg/ml for fosfomycin combined with carbapenems
# The PTA ≥ 90% was considered optimal against a bacterial population, whereas a PTA between 80% and 90% was associated with moderate probabilities of success.

Table 3
%CFR of fosfomycin(FOF) - carbapenems combination regimens ((doripenem (DOM), imipenem (IPM), meropenem (MEM)) of non-MDR PA.

%CFR of combinations	IPM 1 g q 8 h	IPM 1 g in 3 h q 8 h	DOM 1 g q 8 h	DOM 1 g in 4 h q 8 h	MEM 1 g q 8 h	MEM 1 g in 3 h q 8 h	MEM 2 g q 8 h	MEM 2 g in 3 h q 8 h
FOF 4 g q 12 h	19	22	22	23	21	21	21	21
FOF 8 g q 12 h	11	13	12	13	12	12	12	12
FOF 4 g q 8 h	49	53	51	51	51	52	52	52
FOF 4 g q 6 h	65	74	69	72	75	75	75	76
FOF 8 g q 8 h	70	72	76	80	82	82	83	83
FOF 16 g continuous infusion	71	72	83	88	88	88	88	88
FOF 8 g in 6 h q 8 h	75	76	87	93	89	92	93	93

[#]The CFR $\geq$ 90% was considered optimal against a bacterial population, whereas a CFR between 80% and 90% was associated with moderate probabilities of success.

the point that the teaching hospital showing a higher MIC than a general hospital, as indicated in that previous study, might be due to the high antimicrobial consumption rate in the teaching hospital.[51] Our study had 40% of CRPA indicating a high prevalence of carbapenem-non susceptible *P. aeruginosa* in this teaching hospital. Therefore, monotherapy of fosfomycin in our study could not achieve the target indicated above. However, the combination of fosfomycin and carbapenem in our study showed decreased MICs of PA for both drugs. In the CRPA subgroup in our study, the combination of fosfomycin and doripenem decreased the MIC of the doripenem to 2 mg/ml, and the fosfomycin in combination with meropenem decreased the MIC of meropenem by more than a third (Table 1). This was similar to an *in vitro* combination study which found that fosfomycin combined with carbapems decreased the MIC of both drugs together in combination.[19]

PD studies of fosfomycin show a time-dependent killing effect on *Staphylococcus aureus* and *P. aeroginosa*. In contrast, its effectiveness in killing *Escherichia coli* or *Proteus mirabilis* is concentration- dependent activity.[15,18,38] Thus, the most predictive PK/PD parameter of fosfomycin for *P. aeruginosa* eradication is the time that the drug is present in the blood at or above the minimum inhibitory concentration (T>MIC).[18,37,38] The PK/PD targets in this study were chosen for their propensity to achieve the greatest %PTA and %CFR of 70% T>MIC for fosfomycin. However, these targets were determined based on limited information. Basically, effective dosage regimens for all time-dependent antimicrobials require serum drug concentrations exceeding the MIC of the causative pathogen for at least 40 to 70% of the dosing interval in the immunocompetent host,[52–54] although %T>MIC of 70 - 100% is required in difficult-to-treat infections and/or in cases with neutropenia.[47,52,53] These compounds which have the ability to inhibit bacterial cell wall synthesis may be shared with fosfomycin. As well, fosfomycin has a PAE of approximately 0.3-5.5 hours for *P. aeruginosa*.[38] Thus, 70% - 100% of the time above MIC could be appropriate for fosfomycin in the treatment of *P. aeruginosa* in critically ill patients. In addition, there is clear evidence suggesting that carbapenems require a PK/PD target of 40% T>MIC for the treatment of gram-negative infection in critically ill patients.[37–39] For the combination model in our study, we calculated two achievable treatment targets for each patient. First, the 70 - 100% T>MIC of fosfomycin, and second, the PK/PD target of 40% T>MIC for carbapenems. This approach taken in our study has been described in published PK/PD combination model studies.[54]

In our Monte Carlo simulation, we tested both the maximum recommended dose of fosfomycin monotherapy, which is 16 g/day, and also the highest dose of 24 g/day with prolonged or continuous infusion. These simulations were carried out on both non-MDR PA and MDR PA samples. We found that for monotherapy of fosfomycin, neither dosages achieved 80-90% of CFR or PTA in either non-MDR PA or MDR PA. Likewise, other PK studies of fosfomycin in critically ill patients have shown that IV 8 g every 8 hours, with a mean of C_{max} 307 $\pm$ 101 μg/ml,[55] could not achieve the PK/PD target at MIC_{90} (> 1024 μg/ml) when applied to all PA groups in our study. The reason is a higher MIC_{90} of all PA in our study as we discussed above.

However, our study of the combination of fosfomycin with carbapenems in non-MDR PA found that 8 g of fosfomycin given every 8 hours for prolonged infusion over 6 hours in combination with carbapenems showed %PTA or %CFR more than 90%. Fortunately, in CRPA,

the combination of high dose prolonged infusion fosfomycin and doripenem showed greater than 95% PTA at MIC_{90} and approximately 90% CFR. Meropenem in combination with fosfomycin in the CRPA group had 85% CFR but 65% PTA at MIC_{90}. However, 90% PTA of high dose prolonged infusion fosfomycin and meropenem can achieve at MIC_{90} less than 128 μg/ml of fosfomycin and less than 6 μg/ml for meropenem. Fosfomycin in combination with imipenem achieved %PTA and %CFR less than 50% at very high MIC_{90} of imipenem for PA in our study. Thus, empirical therapy for treating PA with area high MIC (less than 128 μg/ml) can use high dose prolonged infusion of fosfomycin and doripenem and a more specific therapy of high dose prolonged infusion of either fosfomycin in combination with doripenem or fosfomycin in combination with meropenem. Our results are similar to those of other PK studies, which calculated that the steady state average concentration (C_{ssave}) of fosfomycin 8 g IV every 8 hours (24 g/day) was 184 μg/ml in the abscess fluid.[56] This level was more than the MIC_{90} (128 μg/ml) in non-MDR PA and CRPA of fosfomycin combined with carbapenems in our study.

Although 24 g/day of fosfomycin in combination might be promising, this high dose may cause adverse side effects. The reported adverse effects from IV fosfomycin in a clinical trial[57] were hypokalemia (26%), followed by pain at the injection site (4%) and heart failure or hypertension (3%). However, some small clinical studies of high dose fosfomycin (24 g) did not show those side effects.[58]

Alternatively, continuous fosfomycin 16 g infusion combination with doripenem 1 g with 4- hour infusion every 8 hours had 80%PTA at MIC_{90} (128 μg/ml) of non-MDR PA or CRPA and CFR was more than 88% at MIC_{90} and 80% at MIC_{90} respectively. Thus, this regimen might be an option for combination therapy when empirically or specifically treating PA with high MIC (less than 128 μg/ml). However, the loading dose of fosfomycin needed in a continuous infusion regimen will apply. Clinical data suggests that prolonged infusions of beta-lactams are effective for gram-negative infections treatment. Meta-analysis studies have found that prolonged infusions of piperacillin-tazobactam in critically ill patients were associated with a mortality benefit compared with intermittent infusions.[27–30]

Our Monte Carlo simulation for monotherapy of fosfomycin might be effective regimen guides (figure 1) when we only know

the MIC of fosfomycin before combinations. A PTA of more than 80 - 90% at MIC less than 32 μg/ml (EUCAST 's susceptibility breakpoint of fosfomycin for *P.aeruginosa*[59]) was achieved by fosfomycin monotherapy of 4 g IV every 8 hours, 8 g IV every 12 hours or higher dose. This is similar to the result from a PK study which showed fosfomycin 8 g IV every 12 hours could achieve a MIC less than 32 μg/ml.[60]

Limitations of this study are as follows. First, we did not simulate the drug level in renally-impaired patients. These patients usually have a high level of drug concentration in the blood which would lower the dosage requirements.[27,43] Second, the isolates of the *P. aeruginosa* were from MIC distributions at the University Hospital, Bangkok, which might be different from those taken from other hospitals or in other countries. These are factors which may well affect the antimicrobial combination of the dose based on the CFR results.[39] Third, the one compartment model used to simulate the fosfomycin level in our study is different from the two compartment model in a recently published article.[61] Nonetheless, for the purpose of calculating T>MIC, there should not be a great difference between these two models. Fourth, our simulation was based on plasma phamacokinetics and not on tissue pharmacokinetics. However, fosfomycin has good penetration to tissue, almost entirely unbound to proteins. Several investigations *in vivo* have confirmed the achievement of a complete concentration equilibrium between plasma and in-tissue fluid shortly after administration. Similarly, PK studies on many tissue levels (skin, urine, lung) showed little difference in plasma.[41,56,62] Therefore, our results might be applicable to those sites of infection. Fifth, fosfomycin PK/PD targets were determined based on limited information but we chose by considering the most important information about compounds which have the ability to inhibit bacterial cell wall synthesis.[47,52,53] Finally, during the period of our study we could not find a previous population PK study of fosfomycin, thus, we chose a PK study of fosfomycin in critically ill patients.

5. Conclusion

The PTA and CFR ≥80- 90% were considered optimal against a bacterial population. Any monotherapy or combination of fosfomycin regimen achieved this target for both of our MDR groups. fosfomycin in combination with imipenem did not achieve this target in any of our PA groups. However, The combination of fosfomycin with doripenem achieved the target especially in CRPA. Fosfomycin in combination with meropem achieved the target, shown only by the CFR result. Therefore, it is suggested that 8 g IV every 8 hours with prolonged infusion of more than 6 hours combination with doripenem 1 g infused 4 hours every 8 hours can be used for non-MDR PA with CRPA with empirical therapy. Optionally, a regimen of continuous fosfomycin 16 g infusion in combination with doripenem could be used. For specific treatment, high dose prolonged infusion of fosfomycin in combination with high dose prolong infusion of meropenem or doripenem (MIC_{90} of combination less than 128 μg/ml for fosfomycin and less than 6 μg/ml for meropenem and less than 2 μg/ml for doripenem) may be necessary.

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