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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