Thai Journal of Pharmacy Practice

RESEARCH ARTICLE

Optimization of Fosfomycin Doses for Treating *Pseudomonas aeruginosa* Infection in Critically Ill Patients by using Monte Carlo Simulation

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Abstract

Objective: To predict appropriate fosfomycin dosing regimens against *P. aeruginosa* infection in critically ill patients. **Method:** Fosfomycin susceptibilities were evaluated by E-test method. The percentages of a 24 h period where the drug concentration exceeded the MIC (T>MIC) of 70% and 100 % and area under the unbound concentration–time curve to MIC ratio (fAUC/MIC) of 489 mg·h/L were used as target values. Monte Carlo simulation was used to calculate T>MIC and fAUC/MIC on day 1 and day 5 of treatment. The probability of target attainment (PTA) and cumulative fraction of response (CFR) were calculated. **Results:** The MICs of fosfomycin were 3 mg/L to > 1024 mg/L. The MIC50 and MIC90 were 64 mg/L and 128 mg/L, respectively. On the first day, the PTAs for achieving 70% T>MIC, 100% T>MIC and fAUC/MIC 489 mg·h/L had reached the target in pathogens with a MIC of 48 mg/L, 32 mg/L, and 4 mg/L in all regimens. The PTAs for achieving PK-PD (pharmacokinetics/pharmacodynamics) targets on day 5 of treatment were reached in *P.aeruginosa* with a MIC of 96 mg/L, 64 mg/L, and 4 mg/L. Using a target CFR of 90%, three out of 16 regimens of fosfomycin were determined to be appropriate for fosfomycin in day 1 of treatment with a PK-PD target of 70% T>MIC. None of fosfomycin regimen achieved a target of 100% T>MIC. On day 5 of treatment, nine and seven regimens gave a CFR >90% of achieving 70% T>MIC and 100% T>MIC, respectively. However, no regimen could achieve the 90% CFR to against *P.aeruginosa* with fAUC/MIC target of 489 mg·h/L either day 1 or day 5 of treatment. **Conclusions:** PTA and CFR did not achieve the target of 90% when fAUC/MIC was used as PK-PD target value. However, when T>MIC was used as target of PK-PD index value, the prolonged or continuous fosfomycin infusion with high dose (24-32 g/day) regimen would be appropriate in first day of treatment. Most of the studied fosfomycin regimens reached the target in day 5.

Keywords: time above MIC, pharmacokinetics, pharmacodynamics, Monte Carlo simulation, fosfomycin

Received: Jun 13, 2019, **Revised manuscript received**: Jul 30, 2019, **Accepted**: Aug 18, 2019

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TJPP Thai Journal of Pharmacy Practice

บทความวิจัย

ขนาดยาฟอสโฟไมซินที่เหมาะสมในการรักษาการติดเชื้อ *Pseudomonas aeruginosa* ในผู้ป่วยวิกฤตโดยใช้การจำลองสถานการณ์ของมอนติคาร์โล

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บทคัดย่อ

วัตถุประสงค์: เพื่อทำนายขนาดยาฟอสโฟมัยซินที่เหมาะสมในการรักษาการติดเชื้อ *P.aeruginosa* ในผู้ป่วยวิกฤต **วิธีการ:** ความไวของเชื้อต่อยาฟอสโฟมัยซินประเมินโดยวิธีการ E-test ค่าเป้าหมายที่ใช้ประเมินประสิทธิภาพการรักษา คือ ร้อยละของระยะเวลาใน 24 ชั่วโมงที่ระดับยาในกระแสเลือดอยู่เหนือค่า MIC (T>MIC) ที่ร้อยละ 70 และ 100 และอัตราส่วนระหว่างพื้นที่ใต้กราฟระหว่างความเข้มข้นของยากับเวลาต่อค่า MIC (*f*AUC/MIC) ที่ 489 มก.·ชม./ลิตร การศึกษาใช้การจำลองสถานการณ์โดยวิธีมอนติคาร์โลในการคำนวณ T>MIC และ *f*AUC/MIC หลังการรักษาในวันที่ 1 และวันที่ 5 การศึกษาคำนวณ probability of target attainment (PTA) และ cumulative fraction of response (CFR) **ผลการวิจัย:** ค่า MIC ของยาฟอสโฟมัยซินอยู่ระหว่าง 3 มก./ลิตร ถึง มากกว่า 1,024 มก./ลิตร ค่า MIC50 และ MIC90 เท่ากับ 64 มก./ลิตร และ 128 มก./ลิตร ตามลำดับ เมื่อกำหนดเป้าหมาย PTA มากกว่าร้อยละ 90 ในวันแรกของการรักษาพบว่า การบริหารยาทุกแนวทางสามารถยับยั้งเชื้อที่มีค่า MIC 48 มก./ลิตร 32 มก./ลิตร และ 4 มก./ลิตรได้เมื่อกำหนดเป้าหมาย T>MIC ที่ร้อยละ 70 และ 100 และ *f*AUC/MIC ที่ 489 มก.·ชม./ลิตร ตามลำดับ และฤทธิ์การยับยั้งเชื้อครอบคลุมที่มีค่า MIC ที่สูงขึ้นเป็น 96 มก./ลิตร 64 มก./ลิตร และ 4 มก./ลิตร ในวันที่ 5 ของการรักษา เมื่อกำหนด CFR เป้าหมายที่ร้อยละ 90 พบว่า ในวันแรกของรักษามีการให้ฟอสโฟมัยซินจำนวน 3 แนวทางจากจำนวนที่ทดสอบทั้งหมด 16 แนวทางสามารถยับยั้งเชื้อตามเป้าหมาย T>MIC ร้อยละ 70 และไม่มีการให้ยาแนวทางใดที่สามารถยับยั้งเชื้อตามเป้าหมาย T>MIC ร้อยละ 100 ได้ แต่เมื่อพิจารณาในวันที่ 5 ของการรักษาพบว่า การบริหารยาฟอสโฟมัยซินจำนวน 9 และ 7 แนวทาง สามารถยับยั้งเชื้อโดยบรรลุเป้าหมาย CFR มากกว่าร้อยละ 90 ได้ที่ T>MIC ที่ร้อยละ 70 และ 100 ตามลำดับ อย่างไรก็ตาม ไม่มีแนวทางการใช้ยาฟอสโฟมัยซินใดที่สามารถยับยั้งเชื้อตามเป้าหมายในวันที่ 1 และ 5 ได้เลยหากใช้ *f*AUC/MIC เป็นค่าเป้าหมายที่ 489 มก.·ชม./ลิตร **สรุป:** การใช้ *f*AUC/MIC เป็นค่าเป้าหมายไม่สามารถทำให้ค่า PTA และ CFR เพียงพอในการยับยั้งเชื้อ *P.aeruginosa* อย่างไรก็ตาม หากกำหนดเป้าหมายการรักษาโดยใช้ค่า T>MIC พบว่า การใช้ยาในขนาดสูง (24-32 กรัม/วัน) ร่วมกับการยืดระยะเวลาในการบริหารยาหรือบริหารยาเข้าหลอดเลือดอย่างต่อเนื่องในวันแรกของการรักษาจะเพิ่มโอกาสให้ระดับยาในกระแสเลือดอยู่ในเป้าหมายมากขึ้น แนวทางการบริหารยาฟอสโฟมัยซินที่ทดสอบมีแนวโน้มที่จะให้ผลลัพธ์ในการรักษาที่ใกล้เคียงกันในวันที่ 5 ของการรักษา

คำสำคัญ: ระยะเวลาที่ระดับยาในกระแสเลือดอยู่เหนือ MIC, เภสัชจลนศาสตร์ เภสัชพลศาสตร์ การจำลองสถานการณ์ของมอนติคาร์โล

Introduction

Fosfomycin has been previously used mainly as an oral treatment for uncomplicated urinary tract infections (UTIs). (1, 2) It inhibits an enzyme-catalyzed reaction in the first step of the cell wall synthesis of both Gram-positive and Gram-negative bacteria. (1, 2) Fosfomycin shows good distribution into tissues reaching sufficient concentrations to eradicate clinically relevant bacteria. (1-3) According to the increasing rate of multidrug-resistant (MDR) infection, parenteral fosfomycin might be a promising revival agent, especially as part of combination therapy for these pathogens for non-UTIs. (1, 2, 4)

Pseudomonas aeruginosa is an important pathogen causing nosocomial infection that is associated with a very high mortality rate. (5, 6) In Thailand, an increasing trend of carbapenem-resistant *P. aeruginosa*, from approximately 10.7% in 2000 to 18.3% in 2018, has become a serious concern due to the lack of effective antimicrobial therapy. (5, 7) The effectiveness of parenteral fosfomycin in combination with other antibiotics for the treatment of non-UTIs from *P.aeruginosa* has been evaluated in several studies which have suggested widely varied doses of fosfomycin. (1, 8, 9) Due to the lack of information regarding appropriate fosfomycin dosing in critically ill patients, the objective of this current study was to predict appropriate parenteral fosfomycin dosing regimens for *P.aeruginosa* infection based on pharmacokinetic-pharmacodynamics (PK-PD) targets in critically ill patients.

Methods

Bacterial strains

All of the clinical *P.aeruginosa* isolates were obtained between August 2014 and April 2015. Each isolate was grown in tryptic soy broth containing 20% glycerol and kept at -80 °C until used. This study protocol was approved with a waiver for informed consent [No. ID0007/2561].

Minimum inhibitory concentration

Minimum inhibitory concentration (MIC) values of fosfomycin were determined using the E-test method. E-test strip supplemented with glucose-6-phosphate (Liofilchem, Italy) was applied on the surface of Mueller-Hinton agar (Difco, USA). The MIC value was read from the scale where the ellipse edge intersects the strip. *Pseudomonas aeruginosa* ATCC 27853 [Department of Medical Sciences Type (DMST) culture collection, Bangkok, Thailand] was used as the positive control. This study investigated MIC range, MIC50, and MIC90 of fosfomycin against *P.aeruginosa*. The MIC range was the difference between the largest and smallest values. MIC50 and MIC90 values were defined as the lowest concentration of fosfomycin at which 50% and 90% of the isolates were inhibited, respectively. According to the breakpoints for fosfomycin against *P. aeruginosa*, we applied modified CLSI breakpoints for *Escherichia coli* with an MIC $\leq$ 64 mg/L considered susceptible and $\geq$ 256 mg/L considered resistant. (10)

Pharmacokinetic-pharmacodynamics model

A simulation was conducted using previously published population pharmacokinetic models of fosfomycin in 12 critically ill patients, and a 2-compartment model was found to be the best base model to fit the data from critically ill patients. (11) The cumulative percentages of a 24 h period that the drug concentration exceeded the MIC (T>MIC) of 70% and 100% were used as a target value of PK-PD (pharmacokinetic-pharmacodynamics) index of fosfomycin. The area under the unbound concentration–time curve to MIC ratio (fAUC/MIC) of 489 mg·h/L was also simulated as target value of PK-PD index.

Monte Carlo Simulation

A total of 10,000 simulated patients were generated by Monte Carlo simulation (MCS) using Oracle Crystal Ball software (Oracle Crystal Ball Classroom Faculty Edition-Oracle 1-Click Crystal Ball 201, Thailand) for each fosfomycin dosing regimen to calculate T>MIC and fAUC/MIC on day 1 to determine fosfomycin level in early phase of treatment and day 5 for steady state level of fosfomycin based on the linear pharmacokinetic behavior.

The efficacy of fosfomycin was assessed for intermittent (30-min) infusion of 8 g q 8 hr, 4 g q 4 h, 4 g q 6 h, and 4 g q 8 hr; prolonged (4-h) infusion of 8 g q 8 h, 8 g q 12 h, 4 g q 6 h, and 4 g q 8 h; continuous (24-h) infusion of 12-, 16-, 20-, and 24-g dose per day. Fosfomycin 4-8 g was given as loading dose (LD) infused for 30 minutes in prolonged and continuous infusion regimens and the maintenance dose (MD) was started immediately after LD.

The probability of target attainment (PTA) was defined by how likely a specific drug dose reached a target PK-PD index. In the present study, target PK-PD indexes were T>MIC 70%, 100% and fAUC/MIC of 489 mg·h/L. The cumulative fraction of response (CFR), the probability of drug dose covering a specified bacterial population, was calculated by the cumulative fraction of proportional bacteria of each fosfomycin MIC multiplied by PTA of each fosfomycin MIC. Dosing regimen reaching above 90% of PTA and CFR was considered the optimal dosage for documented therapy and empirical therapy.

Results

MIC of study isolates

Sixty-three isolates of clinical *P.aeruginosa* were obtained during this study period. The MICs of fosfomycin against *P.aeruginosa* were 3 mg/L to > 1024 mg/L (Figure 1). Fosfomycin susceptibility was graded to be S, I and R in 35, 24 and 4 isolates. The MIC50 and MIC90 for fosfomycin against studied isolates were 64 mg/L and 128 mg/L, respectively.

Probability of target attainment (PTA)

The PTA of the different fosfomycin regimens achieving 70% T>MIC, 100% T>MIC, and fAUC/MIC of 489 mg·h/L at day 1 and day 5 of treatment with fosfomycin are shown in Table 1 and Figure 2. At the first day of treatment, the PTAs for achieving 70% T>MIC, 100% T>MIC, and fAUC/MIC of 489 mg·h/L had reached the target in pathogens with a MIC of 48 mg/L, 32 mg/L, and 4 mg/L in all fosfomycin regimens. The PTAs for achieving 70% T>MIC, 100% T>MIC, and fAUC/MIC of 489 mg·h/L on day 5 increased to reach the target in pathogens with a MIC of 96 mg/L, 64 mg/L, and 4 mg/L, respectively.

Most of the studied fosfomycin regimens reached the PTA target of achieving 70%T>MIC for pathogen with MIC 64 mg/L (MIC50) on day 1. Three regimens of fosfomycin (4 g LD then 24 g infuse 24 h, 8 g LD then 8 g infuse 4 h q 8 h, and 8 g LD then 8 g infuse 4 h q 12 h) covered the pathogen with MIC 128 mg/L (MIC90) at PTAs target of achieving 70% T>MIC. The PTAs above 90% of achieving 100% T>MIC coverage *P.aeruginosa* with MIC 64 mg/L were reached in three regimen (8 g LD then 8 g infuse 4 h q 8 h, 8 g

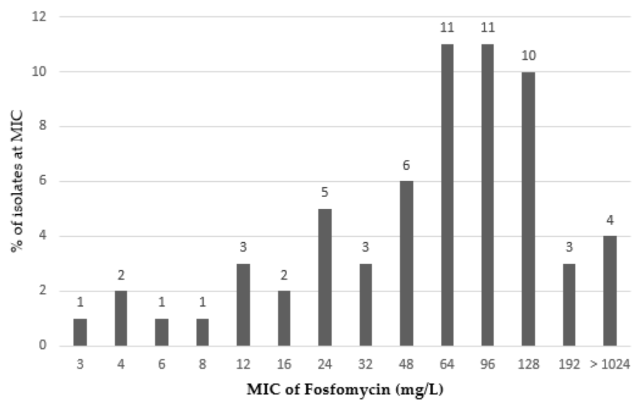

Figure 1. Minimum inhibitory concentrations (MICs) distribution of fosfomycin against *P.aeruginosa* isolates.

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Table 1. Probability of target attainment (PTA) for fosfomycin regimens achieving 70% T>MIC, 100% T>MIC, and *f*AUC/MIC 489 mg·h/L of MIC50 (64 mg/L) and MIC90 (128 mg/L) of *P.aeruginosa* isolates at day 1 and day 5 of treatment

	PTA to achieve T>MIC (%)								PTA to achieve *f*AUC/MIC 489 (%)			
	70%T>MIC (Day 1)		100%T>MIC (Day 1)		70%T>MIC (Day 5)		100%T>MIC (Day 1)		Day 1		Day 5	
	64 mg/L	128 mg/L	64 mg/L	128 mg/L	64 mg/L	128 mg/L	64 mg/L	128 mg/L	64 mg/L	128 mg/L	64 mg/L	128 mg/L
Continuous infusion												
4 g LD then 24 g infuse 24 h	99.85	94.45	65.89	4.33	99.86	98.28	99.86	98.280	0.00	0.00	11.93	0.10
4 g LD then 20 g infuse 24 h	99.66	87.96	65.33	3.85	99.69	96.57	99.69	96.57	0.00	0.00	5.61	0.00
4 g LD then 16 g infuse 24 h	99.29	75.19	64.73	3.74	99.35	94.62	99.35	94.62	0.00	0.00	1.86	0.00
4 g LD then 12 g infuse in 24 h	98.17	52.79	64.5	3	98.26	88.69	98.26	88.69	0.00	0.00	0.10	0.00
Prolonged infusion												
8 g LD then 8 g infuse 4 h q 8 h	99.7	97.79	98.04	61.46	99.40	96.96	98.68	95.31	0.00	0.00	8.09	0.00
8 g LD then 8 g infuse 4 h q 12 h	98.94	93.41	95.15	56.14	98.03	90.92	95.88	86.89	0.00	0.00	1.67	0.00
4 g LD then 4 g infuse 4 h q 6 h	99.13	77.33	63.7	3.41	98.95	93.72	98.22	91.92	0.00	0.00	0.30	0.00
4 g LD then 4 g infuse 4 h q 8 h	97.72	63.78	62.5	3.24	97.03	86.55	95.35	83.7	0.00	0.00	0.00	0.00
Intermittent infusion												
8 g infuse 30 min q 8 h	98.83	86.09	93.84	38.77	99.02	95.59	98.05	93.55	0.00	0.00	8.18	0.00
4 g infuse 30 min q 4 h	99.06	79.8	54.77	0	99.47	97.10	99.19	96.15	0.00	0.00	8.00	0.00
4 g infuse 30 min q 6 h	96.16	42.9	45.36	0	98.16	90.85	96.82	88.40	0.00	0.00	0.49	0.00
4 g infuse 30 min q 8 h	85.91	2.5	37.69	0	95.41	84.74	93.38	81.53	0.00	0.00	0.01	0.00

*f*AUC/MIC; the area under the unbound concentration–time curve to MIC ratio, LD, loading dose; MIC50 and MIC 90, the lowest concentration of fosfomycin at which 50% and 90% of the isolates were inhibited, respectively; PTA, probability of target attainment; q 8 h, every 8 h; T>MIC, the drug concentration exceeds the minimum inhibitory concentration.

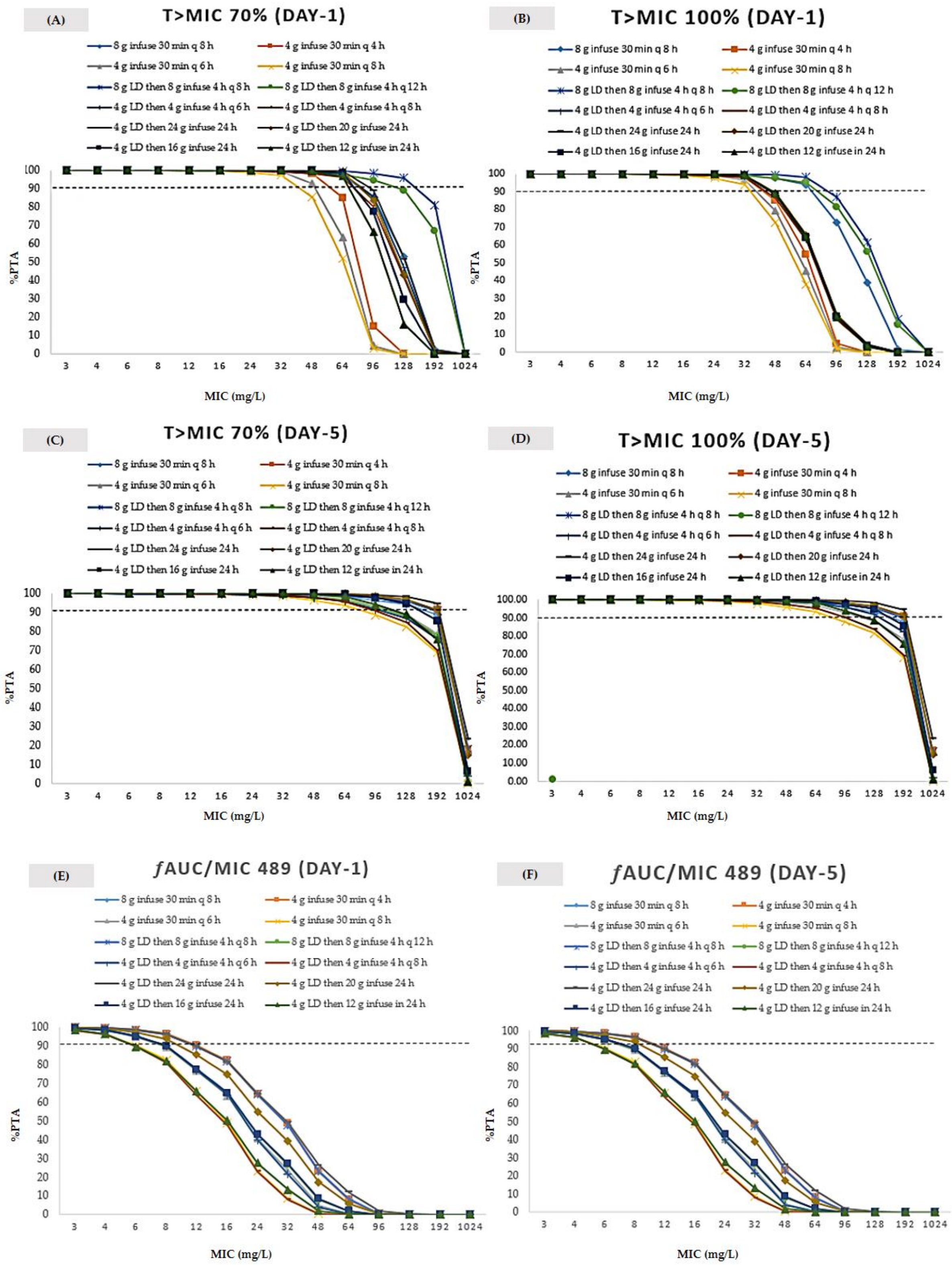

Figure 2. Probability of target attainment (PTA) for fosfomycin regimens achieving T>MIC 70%, 100% and *f*AUC/MIC 489 mg·h/L at day 1 and day 5. (A): 70% T>MIC on day 1; (B): 100% T>MIC on day 1, (C): 70% T>MIC on day 5; (D): 100% T>MIC on day 5; (E): *f*AUC/MIC 489 mg·h/L on day 1; and (F) *f*AUC/MIC 489 mg·h/L on day 5.

LD then 8 g infuse 4 h q 12 h, and 8 g infuse 30 min q 8 h). None of all fosfomycin dosage regimens reached the PTA target of achieving 100% T>MIC coverage *P.aeruginosa* with MIC 128 mg/L at day 1. However, majority of the fosfomycin regimens could achieve the target PTA of 70% T>MIC and 100% T>MIC at day 5 of treatment. When the fAUC/MIC of 489 mg·h/L was used as PK-PD target value of fosfomycin, there was no regimen could achieve the 90% PTA against *P.aeruginosa* with MIC above 64 mg/L either day 1 or day 5 of treatment.

Cumulative fraction of response (CFR)

Using a target 70% T>MIC, three regimens of fosfomycin (4 g LD then 24 g infuse in 24 h, 8 g LD then 8 g infuse 4 h q 8 h, and 8 g LD then 8 g infuse 4 h q 12 h) were determined to be appropriate for fosfomycin in day 1 of treatment with CFR above 90%. None of all fosfomycin dosage regimens reached the CFR target of achieving 100% T>MIC coverage *P.aeruginosa* at day 1. At day 5 of treatment, nine and seven regimens gave a CFR >90% of achieving 70% T>MIC and 100% T>MIC, respectively. However, no regimens could achieve the 90% CFR to against *P.aeruginosa* with fAUC/MIC target of 489 mg·h/L either day 1 or day 5 of treatment. (Table 2)

Discussion

Sepsis and septic shock are common medical conditions in critically ill patients, affecting millions of people around the world each year with a mortality rate as high as 25% or more. (12) Dosing strategies of antimicrobials based on PK-PD principles and specific

Table 2. Cumulative fraction of response on day 1 and day 5 of fosfomycin treatment.

	Day 1			Day 5		
	70% T>MIC	100% T>MIC	fAUC/MIC 489 (%)	70% T>MIC	100% T>MIC	fAUC/MIC 489 (%)
Continuous infusion						
4 g LD then 24 g infuse in 24 h	90.39	52.79	11.41	94.47	94.45	27.03
4 g LD then 20 g infuse in 24 h	88.11	52.66	9.86	93.31	93.29	23.06
4 g LD then 16 g infuse in 24 h	84.56	52.31	8.31	91.96	91.94	19.22
4 g LD then 12 g infuse in 24 h	78.87	52.18	6.91	89.35	89.34	15.07
Prolonged infusion						
8 g LD then 8 g infuse 4 h q 8 h	92.54	80.94	14.37	93.60	92.65	25.71
8 g LD then 8 g infuse 4 h q 12 h	90.72	78.21	12.07	91.32	90.51	19.08
4 g LD then 4 g IV infuse 4 h q 6 h	84.99	52.01	8.56	90.36	88.11	17.93
4 g LD then 4 g infuse 4 h q 8 h	81.06	51.23	7.27	88.18	86.67	14.09
Intermittent infusion						
8 g infuse 30 min q 8 h	87.37	73.07	10.62	92.97	91.78	25.82
4 g infuse 30 min q 4 h	85.44	46.93	9.73	93.65	93.10	25.82
4 g infuse 30 min q 6 h	75.53	44.25	6.72	90.20	88.91	18.15
4 g infuse 30 min q 8 h	59.15	41.82	5.42	87.08	85.28	14.32

LD, loading dose; q 8 h, every 8 h; T>MIC, the drug concentration exceeds the minimum inhibitory concentration; fAUC/MIC, the area under the unbound concentration–time curve to MIC ratio.

drug properties were suggested to improve outcomes in those patients. (12) In critically ill patients, volume of distribution (Vd) of antimicrobials is significantly larger compared to that of non-critically ill patients, and a higher dose is needed to achieve therapeutic level at the site of infection. (12-14)

Fosfomycin is currently being used in combination with other antimicrobials as a last-line treatment in critically ill patients for the treatment of serious infections. (2, 15, 16) The information regarding the use of fosfomycin in combined with other antimicrobials from prospective and retrospective study reveals a favorable clinical cure rate ranging from approximately 54.2 to 87.5%. (17) The common adverse effects found from fosfomycin were hypernatremia, hypokalemia, acute kidney injuries, and abnormal liver function test. (17) It has an extremely low molecular weight, and shows almost no binding to proteins so the apparent Vd of fosfomycin in critically ill patients revealed higher than that observed in healthy volunteers (48.8 liters vs 22 liters). The plasma level of fosfomycin, especially in early phases of treatment, had a subtherapeutic effect in critically ill patients. (2, 15)

In our study, fosfomycin 4-8 g was given as an initial dose for all regimens and the maintenance dose (MD) was started immediately after the loading dose to yield optimal PK-PD parameters in prolonged and continuous infusion regimens. The efficacy of fosfomycin was also assessed in day 5 of treatment to determine the treatment effect at a steady state. Pharmacodynamic studies of fosfomycin show a time-dependent killing effect on *P. aeruginosa*, so the 70% T>MIC was used as PK-PD targets for fosfomycin in Asuphon study. (8) However, a study from Bilal reported the bacterial killing of fosfomycin against *P. aeruginosa* was most closely associated with the area under the unbound concentration–time curve to MIC ratio (fAUC/MIC). The fAUC/MIC targets required to achieve 1 log10 reductions in the area under the cfu/mL curve relative to growth control were 489. (18) Based on limited information regarding optimal PK-PD targets for fosfomycin, we used 70% T>MIC (8) and fAUC/MIC of 489 mg·h/L as our key PK-PD targets. We also used 100% T>MIC as our PK-PD target since it might be associated with favorable outcomes in critically ill patients who had severe infections. (12)

In our study, the MICs of fosfomycin for *P. aeruginosa* were within the range of 3 mg/L to > 1024 mg/L. The MIC50 and MIC90 were 64 mg/L and 128 mg/L, respectively. Since the breakpoint for fosfomycin against *P.aeruginosa* is lacking, we used CLSI breakpoints for *E.coli* with an MIC ≤ 64 mg/L to consider susceptibility. Fifty percent of *P. aeruginosa* isolates in our study were graded to be susceptible to fosfomycin, a percentage comparable to previous studies. (4) At day 1 of treatment, the favorable T>MIC parameters of fosfomycin was observed in high dose (24-32 g/day) with prolonged or continuous infusion regimens for covering *P.aeruginosa* isolates with MIC50 of 64 mg/L. Majority of fosfomycin regimens (12–24 g/day), including intermittent, prolonged and continuous infusion, yield the optimum PK-PD parameter in day 5 of treatment. However, when we used fAUC/MIC target of 489 mg·h/L as our PK-PD target there were no regimens achievind the PTA and CFR to against *P.aeruginosa* either day 1 or day 5 of treatment.

Several limitations may be identified in our study, including how we predicted the efficacy of fosfomycin regimens as monotherapy would not directly apply to our results in a combination regimen of fosfomycin with other antimicrobials. However, the data from *in vitro* synergy studies reported synergistic activities of fosfomycin combined with several antimicro-bials (19-21), so the suggested dosage of fosfomycin from our study might have a positive effect in combination regimen. We did not determine the adverse drug reaction of a high dose regimen of fosfomycin especially on day 1 of treatment that required 24-32 g to achieved PK-PD target; another clinical study should be performed to confirm this. Lastly, our results could not apply to the critically ill patients with renal impairment because the majority of patients (10 of 12 critically ill patients) in the Parker study had normal renal function. (15)

In conclusion, in the first day of treatment, the favorable T>MIC parameters of fosfomycin in critically ill patients were observed in high dose (24-32 g/day) with prolonged or continuous infusion regimens for covering *P.aeruginosa* isolates where MIC lower than 64 mg/L. Lower dose of fosfomycin regimen yields the optimum PK-PD parameter in day 5 of treatment in intermittent, prolonged and continuous infusion. The PTA and CFR did not achieve the target of 90% when fAUC/MIC of 489 mg·h/L was used as PK-PD target value.

Acknowledgement

This research was supported by a grant from Phayathai II International Hospital. We thank our English facilitator, Ms. Maria Mullet from the Faculty of Phramaceutical Sciences, Prince of Songkla University for editing our manuscript. Thanks also to Dr. Weerayuth Saelim and Dr. Jatapat Hemapanpairoa who provided insight and expertise that greatly assisted the research.

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