Comparison of Continuous Infusion versus Intermittent Infusion of Vancomycin in Patients with Methicillin-Resistant *Staphylococcus aureus*

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Objective: *To compare the pharmacokinetics of vancomycin administration by continuous infusion and intermittent infusion.*
Material and Method: *A prospective, randomized, two-way crossover study of 12 patients with methicillin-resistant Staphylococcus aureus infections was conducted. All patients were randomized to receive vancomycin in both regimens consecutively: (i) infusion of 15 mg/kg of vancomycin as a loading dose for 1 h followed by 30 mg/kg of vancomycin as a continuous infusion over 24 h for 48 h; and (ii) intermittent infusion of 15 mg/kg of vancomycin for 1 h every 12 h for 48 h. Vancomycin pharmacokinetic studies were carried out during hours 24-48 after the start of both regimens.*
Results: *For the continuous infusion regimen, the mean highest steady-state concentration was 24.88 $\pm$ 12.75 μg/ml and the mean lowest steady-state concentration was 19.89 $\pm$ 10.15 μg/ml. For the intermittent infusion regimen, the mean peak and trough serum concentrations were 55.02 $\pm$ 17.36 and 12.43 $\pm$ 12.86 μg/ml, respectively. After 10 days of vancomycin treatment, the MRSA infections were eradicated in all patients. Moreover, during both methods of infusion, no adverse events related to the use of vancomycin were observed.*
Conclusion: *Either continuous infusion or intermittent infusion can be used as an effective mode of vancomycin administration to achieve bactericidal activity.*

Keywords: *Vancomycin, Continuous infusion, Intermittent infusion*

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Over the last decade, several investigators have attempted to establish the most appropriate administration technique to optimize bactericidal activity of parenteral antibiotics. Although intermittent infusion of antimicrobial agents following manufacturer's instructions is the standard clinical practice, continuous infusion has been proposed as an alternative mode of administration to improve the maximal bactericidal effect. Vancomycin, a glycopeptide antibiotic, is one of the antibiotics currently used worldwide for the treatment of infections caused by gram positive pathogens, including multidrug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococci[1]. Following the manufacturer's instructions, this agent is usually administered by either 500 mg every 6 h or 1000 mg every 12 h intermittent infusion of at least 1 h to minimize infusion-related adverse effects. The objective of the present study was to compare the pharmacokinetics of vancomycin administration by continuous infusion and intermittent infusion.

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Material and Method

Subjects

The present study was conducted in patients with MRSA infection. The patients were eligible for the present study if they met the following criteria: (i) older

than 18 years; and (ii) documented MRSA infection. The biochemical and antimicrobial susceptibility test were used for identifying MRSA and the MICs were determined by E-test. The protocol for the present study was approved by the Ethics Committee of Songklanagarind Hospital and written informed consent was obtained from each patient. None of the patients had a chronic illness or was taking chronic medication. Patients were excluded from the present study if they were pregnant or in circulatory shock (which was defined as a systolic blood pressure of < 90 mmHg and poor tissue perfusion) or had documented hypersensitivity to vancomycin or an estimated creatinine clearance (determined by the Cockcroft-Gault method) of < 60 ml/min[2].

Drugs and chemicals

Vancomycin (Vancin-S®) was generously donated by Siam Pharmaceutical, Thailand. All of the solvents were HPLC grade.

Study design

The present study was a prospective randomized two-way crossover study. Vancomycin was reconstituted according to the manufacturer's guidelines and diluted to a concentration of 0.25 mg/kg/ml in 5% dextrose in water. All patients were randomized to receive vancomycin in both regimens consecutively: (i) infusion of 15 mg/kg of vancomycin as a loading dose for 1 h followed by 30 mg/kg of vancomycin as the continuous infusion over 24 h via an infusion pump at a constant flow rate for 48 h; and (ii) intermittent infusion of 15 mg/kg of vancomycin for 1 h via an infusion pump at a constant flow rate every 12 h for 48 h. After vancomycin therapy for 4 days in the present study, all patients still received vancomycin for six more days to complete the course of treatment of 10 days.

Blood sampling

For both regimens, vancomycin pharmacokinetic studies were carried out during 24-48 h after the start of the each regimen. For the continuous infusion regimen, blood samples of approximately 2 ml per time were obtained by direct venepuncture at 24, 30, 36, 42, and 48 h, and for the intermittent infusion regimen, blood samples of approximately 2 ml per time were obtained by direct venepuncture at 24, 25, 36, 37, 38, 39, 40, 42, 44, and 48 h.

All blood samples were allowed to clot and then centrifuged at 2000 g. The serum obtained was stored at -80°C until analysis.

Table1. The characteristics of the 12 patients and the MIC of vancomycin for isolated pathogens

Patients	Sex	Age (years)	Body weight (kg)	Diagnosis	Creatinine clearance (ml/min)	Isolated specimen	Pathogen	MIC (μg/ml)
S-K	Female	19	50	Neurilemoma and ventilator associated pneumonia	134.76	Sputum	MRSA	1.5
P-P	Male	37	55	Chronic osteomyelitis	94.80	Bone	MRSA	1.0
S-P	Male	23	65	Severe head injury	153.08	Blood	MRSA	1.5
S-B	Male	76	50	Ischemic heart disease	88.89	Blood	MRSA	1.5
N-C	Male	48	65	Chronic obstructive pulmonary disease and ventilator associated pneumonia	67.39	Sputum	MRSA	1.0
P-S	Male	87	65	CA esophagus	156.71	Blood	MRSA	1.0
B-G	Male	18	40	Bedsore	150.62	Pus	MRSA	1.0
L-A	Female	66	60	Ventilator associated pneumonia and bacterial meningitis	109.20	Blood	MRSA	1.0
T-D	Male	77	70	Chronic obstructive pulmonary disease and aspiration pneumonia	111.36	Blood	MRSA	1.5
A-C	Male	32	50	Ventilator associated pneumonia	84.27	Sputum	MRSA	1.5
S-S	Female	47	55	Wound at right leg	94.35	Pus	MRSA	1.5
S-G	Male	38	65	Chronic osteomyelitis	94.98	Bone	MRSA	1.5

Vancomycin assays

Concentrations of vancomycin in serum were determined by fluorescence polarization immunoassay (AxSYM; Abbott Laboratories, Abbott Park, IL 60064 USA). The assay limit of detection of vancomycin was 2 μg/ml and the intraday and interday assay coefficients of variation were < 7% over the entire calibration range (7 to 75 μg/ml).

Pharmacokinetic and statistical analysis

The results were expressed as mean ± standard deviations. Pharmacokinetic analysis was conducted using a non-compartment model. The maximum serum concentrations (C_{max}), the minimum serum concentrations (C_{min}), the elimination half-life ($t_{1/2}$), the elimination rate constants (k_{el}), the areas under the concentration-time curve between 0 and 24 h (AUC_{0-24}), the total clearances (CL_{tot}) and the volumes of distribution (V) were determined using WinNonlin Version 1.1 (Scientific Consulting Inc., NC, USA).

Results

Twelve patients were enrolled in the present study, nine male and three female. The characteristics of all patients and the MICs of vancomycin for the isolated pathogens are shown in Table 1. The mean serum vancomycin concentration-time data for continuous infusion and intermittent infusion from each patient are shown in Fig. 1. The pharmacokinetic parameters for the two regimens are presented in Table 2. In both regimens, the serum vancomycin concentrations at all time points were higher than the MIC for the isolated pathogens in the present study. No adverse effects were observed in any patient during the study period.

Table 2. Pharmacokinetic parameters (mean ± SD) of vancomycin administered by continuous and intermittent infusion regimen

Parameter (units)	Continuous infusion	Intermittent infusion
C_{max} (μg/ml)	24.88 ± 12.75	55.02 ± 17.36
C_{min} (μg/ml)	19.89 ± 10.15	12.43 ± 12.86
AUC_{0-24} (μg x h/ml)	502.99 ± 261.25	631.80 ± 333.18
CL_{tot} (liter/h)	-	1.46 ± 0.88
$t_{1/2}$ (h)	-	15.40 ± 19.10
k_{el} (h^{-1})	-	0.17 ± 0.18
V (liter)	-	17.57 ± 6.64

C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; AUC_{0-24}, area under the concentration-time curve between 0 and 24 h; CL_{tot}, total clearance; $t_{1/2}$, serum half-life; k_{el}, elimination rate constant; V, volume of distribution

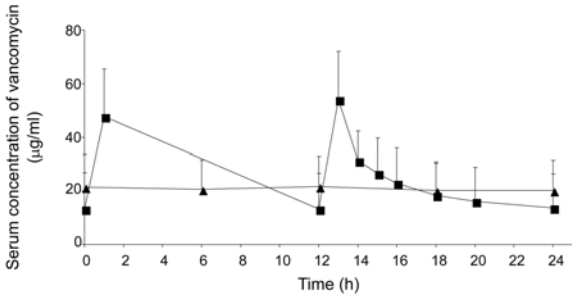

Fig. 1 Mean serum vancomycin concentration-time data for the twelve patients with MRSA infection following administration of continuous infusion regimen (filled triangles) and intermittent infusion regimen (filled squares)

Discussion

Antimicrobial agents have two primary patterns of microbial killing[3]. The first pattern is characterized by concentration-dependent bacterial killing. Aminoglycosides and fluoroquinolones, for example, have been found to exhibit this pattern of killing, and increasing the peak serum drug concentration enhances the bactericidal activity of these agents[3,4]. The second pattern is characterized by time-dependent bacterial killing. Therefore, the time that concentrations in tissue and serum are above the MIC (t > MIC) is the pharmacokinetic/pharmacodynamic (PK/PD) index that correlates with efficacy. This pattern is observed, for instance, with β-lactam antibiotics, glycopeptides, macrolides, and clindamycin[3,5,6].

Vancomycin belongs to the second group, and exhibits time-dependent bacterial killing of gram positive organisms[7]. In vitro and neutropenic mouse thigh infection models have demonstrated that the area under the concentration curve (AUC) divided by the MIC (AUC/MIC) appears to be the best predictor of the activity of vancomycin against MRSA[7]. An AUC/MIC value of ≥ 400 was associated with a successful outcome when compared with an AUC/MIC value of < 400[8]. However, another previous study in patients with gram positive infections was conducted to compare a target concentration of 15 μg/ml via continuous infusions versus peak and trough concentrations of 25 to 35 and 5 to 10 μg/ml,

respectively, via conventional dosing of 1 g every 12 h of vancomycin. It has been found that both methods of intravenous administration revealed equivalent pharmacodynamic activities of vancomycin[9]. The present findings in critically ill patients with MRSA infections also confirmed the previous study. For the continuous infusion regimen, all patients received 15 mg/kg of vancomycin as a loading dose at the start of a 24-hour regimen of 30 mg/kg of vancomycin through continuous infusion. The serum concentrations obtained from this loading dose were high enough to ensure the rapid onset of antibacterial activity and the continuous infusion regimen provides mean lowest steady-state serum concentrations of approximately 20 μg/ml throughout the dosing interval. For the intermittent infusion regimen, the mean peak and trough serum concentrations were approximately 55 and 12 μg/ml, respectively.

The outcome of vancomycin treatment by continuous infusion and intermittent infusion in the present study could not be evaluated because the drug treatment by both modes of administration were infused consecutively in each patient. However, after 10 days of vancomycin treatment, the MRSA infections were eradicated in all patients. Moreover, during both methods of infusion, no adverse events related to the use of vancomycin were observed.

In conclusion, either continuous infusion or intermittent infusion can be used as an effective mode of vancomycin administration to achieve bactericidal activity.

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ศึกษาเปรียบเทียบการบริหารยา vancomycin ด้วยวิธี continuous infusion และ intermittent infusion ในผู้ป่วยติดเชื้อ methicillin-resistant Staphylococcus aureus

สุเทพ จารุรัตนศิริกุล, จักราวดี จุฬามณี, ธีรทัศน์ สุดสาย, พันธ์วศรี แสงสุวรรณ, มนชนา จุลลางกูร, ณัฐณิชา อิงวิยะ, รุ่งเรือง จารุมโนกุล

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบค่าเภสัชจลนศาสตร์ของ vancomycin เมื่อบริหารด้วยวิธี continuous infusion และ intermittent infusion*

วัสดุและวิธีการ: *การศึกษาแบบไปข้างหน้าด้วยวิธีการสุ่มแบบข้ามสลับในผู้ป่วยติดเชื้อ methicillin-resistant Staphylococcus aureus จำนวน 12 ราย ผู้ป่วยทุกรายจะถูกสุ่มให้ได้รับ vancomycin ก่อนและหลังกัน 2 วิธี โดยให้ติดต่อกัน ดังนี้ วิธีที่ 1 บริหารยาในขนาด 15 มิลลิกรัม/กิโลกรัม นาน 1 ชั่วโมง เป็น loading แล้วตามด้วยวิธี continuous infusion ในขนาดยา 30 มิลลิกรัม/กิโลกรัม ในเวลา 24 ชั่วโมง เป็นเวลา 48 ชั่วโมง และวิธีที่ 2 บริหารยาด้วยวิธี intermittent infusion นาน 1 ชั่วโมง ในขนาด 15 มิลลิกรัม/กิโลกรัม ทุก 12 ชั่วโมง เป็นเวลา 48 ชั่วโมง ศึกษาทางด้านเภสัชจลนศาสตร์ของ vancomycin ในช่วงเวลา 24-48 ชั่วโมง หลังเริ่มยาทั้ง 2 วิธี*

ผลการศึกษา: *เมื่อบริหารยาด้วยวิธี continuous infusion ค่าความเข้มข้นเฉลี่ยสูงสุดที่ steady state เท่ากับ 24.88 $\pm$ 12.75 ไมโครกรัม/มิลลิลิตร และค่าความเข้มข้นเฉลี่ยต่ำสุดที่ steady state เท่ากับ19.89 $\pm$ 10.15 ไมโครกรัม/มิลลิลิตร เมื่อบริหารยาด้วยวิธี intermittent infusion ค่าความเข้มข้นเฉลี่ยสูงสุดและต่ำสุดเท่ากับ 55.02 $\pm$ 17.36 and 12.43 $\pm$ 12.86 ไมโครกรัม/มิลลิลิตร ตามลำดับภายหลังการรักษาผู้ป่วยต่อจนครบ 10 วัน เชื้อ MRSA ถูกกำจัดออกจากร่างกายของผู้ป่วยทุกราย นอกจากนั้นในระหว่างการบริหารยาทั้ง 2 วิธี ไม่พบผลข้างเคียง ที่เกี่ยวข้องกับยา vancomycin*

สรุป: *การบริหาร vancomycin วิธี continuous infusion หรือ intermittent infusion สามารถใช้เป็นวิธีการบริหารยาได้อย่างมีประสิทธิภาพเท่าเทียมกัน*