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Amikacin: Area Under Curve for Once Daily Dose and Its Correlation with Plasma Concentration at Six Hours Post Infusion

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Abstract : **Aminoglycosides are commonly used for gram-negative septicemia. Formerly, peak and trough plasma levels were the monitoring parameters for conventional dose which was every eight hours. At present the recommended dose is once daily and the recommended monitoring parameters are the area under concentration time curve and the six-hour plasma concentration post-infusion. This report recommends a 163.52 milligrams per liter-hour (range 146-180) for the area under curve and 6.79 milligrams per liter (range 5.6-7.9) for the six-hour plasma concentration post-infusion. The correlation of the area under curve and the six-hour plasma concentration post-infusion was reported in a linear equation with significance.**

Key words : Aminoglycosides, Amikacin, Area under curve.

เรื่องย่อ : อามิกาซิน : พื้นที่ใต้กราฟสำหรับขนาดที่ใช้วันละครั้งและความสัมพันธ์กับระดับยาในเลือดที่เวลาหกชั่วโมงหลังบริหารยา

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อามิโนไกลโคไซด์ เป็นยาปฏิชีวนะที่ใช้บ่อยทางคลินิกโดยเฉพาะกับเชื้อกรัมลบ พิษส่วนใหญ่ที่เกิดจากยาปฏิชีวนะกลุ่มนี้คือพิษต่อไต ซึ่งแต่เดิมให้ยาในขนาดน้อยและให้ห่างทุก 8 ชั่วโมง และมีการตรวจวัดระดับยาในเลือดหาระดับสูงสุดและต่ำสุดเพื่อช่วยลดอันตรายจากการได้รับยาเกินขนาด ปัจจุบันมีการแนะนำให้ใช้ยากลุ่มดังกล่าวในขนาดมากขึ้นแต่ให้เพียงวันละครั้งเดียว โดยมีจุดประสงค์เพื่อลดการสะสมของยาลง การตรวจเพื่อหาระดับสูงสุดและต่ำสุดถูกลดความสำคัญลงตามลำดับ การตรวจทางห้องปฏิบัติการที่ได้รับคำแนะนำต่อมาสำหรับการให้ยาวันละครั้งเดียวคือการหาพื้นที่ใต้กราฟของยานั้นๆ และการหาความเข้มข้นของยาที่ 6 ชั่วโมงหลังฉีดเข้าหลอดเลือดดำเพื่อใช้ในการติดตามการใช้ยานั้นๆ ผลจากการศึกษาพบว่า พื้นที่ใต้กราฟของยาอามิกาซิน ขนาด 500 และ 750 มิลลิกรัมต่อวัน มีค่าไม่ต่างกันและเท่ากับ 163.52 หน่วยพื้นที่ และพบว่ามีความสัมพันธ์เชิงเส้นตรงกับค่าความเข้มข้นของยาในเลือดที่ 6 ชั่วโมงหลังบริหารยา ผลการศึกษาดังกล่าวจะเป็นประโยชน์สำหรับการศึกษาเพื่อลดอันตรายต่อไตจากการใช้ยาในขนาดสูงต่อไป

INTRODUCTION

Aminoglycosides are antibiotics commonly used in the hospital practice. Survival of patients with gram-negative septicemia depends upon the extent of the underlying disease and the early use of appropriate antibiotics. Duration of treatment in serious infection is typically more than two weeks of intravenous injections. Because of the physiologic changes in drug disposition and the elimination occur with severe gram-negative sepsis, a pharmacokinetic model has been developed from serum concentration and time data which individualizes the dosage and the dosage interval for a patient[1-6]. Amikacin is excreted almost entirely by renal mechanisms. Its use in patients with renal function impairment has resulted in accumulation and is associated with nephrotoxicity[6-10]. To avoid this potential toxicity in the patient with prolonged use of these antibiotics, a dosage adjustment has been devised[1-3,7-9]. In the past, recommended peak and trough concentrations were published in standard literatures for the prevention of toxicity with conventional usage[6,8,10]. Recently, once-daily aminoglycoside administration was recommended in septicemic patients because of its post-antibiotic effect (PAE) and the very low trough level indicating reduced toxicity[1,11-15]. However, evidences of nephrotoxicity and ototoxicity still remain in the patients who use a once-daily dose regimen. The area under the curve (AUC) has been suggested to be a new method for monitoring a once-daily dose regimen for aminoglycosides. The pharmacokinetic results of the area under curve (AUC) are different for every eight hours dosing and a once-daily dosing[1,14,15]. Furthermore, the area under curve (AUC) of the once-daily dose was found to be possibly much larger than the respective area under the curve of the conventional dose[1,13]. Note that, the parameters of the area under the curve of Amikacin have not been previously published in any literature. The recommended doses were always justified by creatinine clearance. The most widely used dosages are 500 mg per day and 750 mg per day[16-21]. In this report we studied the area under the curve of the widely recommended doses of Amikacin (500 mg per day and 750 mg per day) with respect to the concentration at six hours post-infusion.

MATERIALS AND METHODS

We used data acquired from studies of two different dosages of Amikacin (500 mg per day and 750 mg per day) to develop the area under the curve described below.

The study involved 47 patients who received Amikacin by intravenous infusion, 13 patients received a 500 mg per day and 34 patients received a 750 mg per day. All patients participating in this study gave written informed consent as required by the Ethics Committee (Faculty of Medicine Siriraj Hospital, Mahidol University).

First, the blood was taken from the patients at the end of infusion and at six hours post-infusion. The Amikacin concentration analysis was done using a TDX (fluorescence polarization immunoassay) instrument with specified Amikacin reagent availble from the ABBOTT Company (Thailand). Then, we calculated the following:-

The predicted concentration in mg per litre of Amikacin at first hour, the predicted concentration at 24 hours and the constant value of elimination (K) using Sawchuk-Zaske's equation[2].

1. The constant value of the elimination (K):

$K = (\ln C_1 - \ln C_2) / t_2 - t_1$

C_1 = concentration at 1 hr

C_2 = concentration at 6 hr

T_1 = 1 hr after infusion

T_2 = 6 hr after infusion

2. The predicted concentration at the end of infusion (C_{end}):

$(C_{end}) = C_1 / e^{-k(t_1 - t_{end})}$ (T_{end}= duration of infusion)

3. The predicted concentration at 24 hours (C_{24})

$C_{24} = C_2 \times e^{-k(24-t_2)}$

The area under the curve was calculated using Begg and Barclay's formula[1].

4. The area under the curve over the 24 hours dose interval AUC(0,24), assuming a half-hour infusion time:

AUC (0,24) = AUC (end, 24) + AUC infusion

AUC (0,24) = $[(C_{end} - C_{24}) / k] + [0.065 \times (C_{end} - C_{24}) / k]$

(0.065 is the constant value within Begg and Barclay's formula[1])

The differences between areas under the curve among these two dosage groups and their correlation were separately reported in the following results.

RESULTS

Thirty male patients and 17 female patients participated in this study. Patients' ages ranged between 14-76 years and the mean age of the patients was 48.1 years. The majority of the patients were over 40 years old and over. The lengths of stay in hospital ranged from 2-40 days, with a mean of 15 days.

Thirteen patients received a once daily 500 mg dose of Amikacin and 34 patients received 750 mg dose of Amikacin by intravenous infusion. The calculated area under the curve in this study was 155.69 mg per liter-hour for a 500 milligram daily dose (range 115 to 195 mg per liter-hour) and 166.52 mg per liter-hour for 750 mg once daily dose (range 146 to 186 mg per liter-hour). The mean Amikacin plasma concentration at six hours was 7.46 mg per liter and 6.54 mg per liter respectively (Table 1). The correlation between the area under curve and creatinine clearance was determined. Results are shown in Table 2 and reported significant in correlation. At the same time, the correlation between the area under the curve and the plasma concentration at six hours was reported to be 0.918 which was significant (Table 2). The linear regression was determined by statistical analysis and was significant for the plasma concentration at six hours post-infusion.

Plasma concentration at six hours after infusion was linearly correlated with the area under the curve by the coefficient of determination R^2 of 0.843 (Table 3) and is showed as a line graph in Figure 1. The equation used for calculation of correlation between the area under curve and the concentration at six hours post-infusion was AUC = (13.661 x the concentration at six hours) + 70.706.

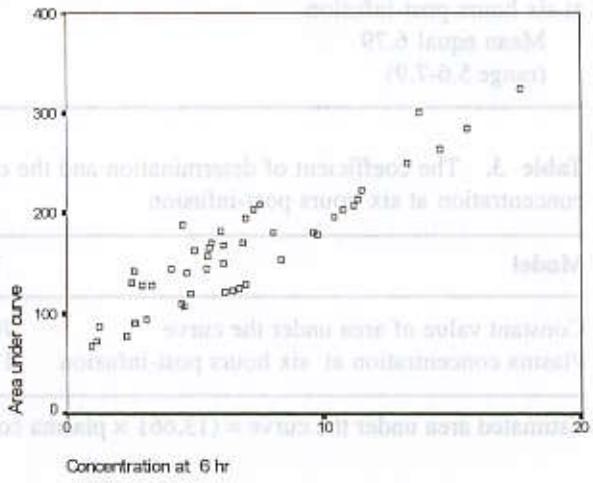

Figure 1. The relationship between the plasma concentration at six hours post-infusion and the area under the curve. (Data figured from both 500 mg per liter and 750 mg per liter)

Table 1. Mean and equal variance assumed of the area under curve, plasma concentration at 6 hours post-infusion of 500 mg and 750 mg daily dosages and creatine clearance before infusion

Parameter	Dose = 500 mg/day (n =13)	Dose = 750 mg/day (n = 34)	Both 500 and 750 mg/day (n = 47)	Equal variance assumed Sig (2-tailed)
Area under curve	155.69 (range 115-195)	166.52 (range 146-186)	163.52 (range 146-180)	0.58
Concentration at 6 hours	7.46 (range 4.7-10.1)	6.54 (range 5.2-7.8)	6.79 (range 5.6-7.9)	0.607
Creatinine clearance	0.134 (range 0.084 - 0.185)	0.144 (range 0.125 - 0.163)	0.141(range 0.122 - 0.160)	0.711

Table 2. The correlation and linear regression of the creatinine clearance and concentration at six hours post-infusion with the area under curve

Correlation (n = 47)	Area under the curve of both 500 and 750 mg/L Mean equal 163.52 (range 146 - 180)	Correlation significant (2 tailed) (at level 0.01)	Linear regression significant
Creatinine clearance Mean equal 0.141 (range 0.122-0.160)	-0.391	0.007	0.528
Plasma concentration at six hours post-infusion Mean equal 6.79 (range 5.6-7.9)	0.918	0.000	0.000

Table 3. The coefficient of determination and the constant value of the area under curve predicted by the concentration at six hours post-infusion

Model	Beta	Significant	R square
Constant value of area under the curve	70.706	0.000	-
Plasma concentration at six hours post-infusion	13.661	0.000	0.843

Estimated area under the curve = (13.661 × plasma concentration at six hours post-infusion) + 70.706

DISCUSSION

In this study, the area under the curve of Amikacin was calculated from the study of a 500 mg and a 750 mg once daily dose. A previous study of Amikacin by Hassan et al[7] estimated the area under curve from a conventional dose only. The area under the curve was developed for monitoring the once daily Amikacin which differed from monitoring the conventional infusion in which peak and trough values were used. The method was recommended by Begg et al[1]. The parameters of this study show the correlation of the commonly recommended dose of Amikacin (500 and 750 mg per day) in Thailand between the area under curve and other parameters, i.e. creatinine clearance and plasma Amikacin concentration at six hours post-infusion.

The creatinine clearance is the first parameter that physicians use in adjusting the daily dosage. In this study, we recorded the creatinine clearance and found that there was no significant difference of this parameter between the regimens of 500 mg and 750 mg per day. Meanwhile, physicians look for some other criteria for choosing a dosage of Amikacin other than data from creatinine clearance.

There was no difference in the area under the curve between these two dosage regimens. Thus, the mean value of the area under curve of 163.52 mg per liter-hour can be used as the recommended value in any further studies in which the common dosages are 500 and 750 mg per day. Whether the greater the area under the curve, the more likely nephrotoxicity occurs, needs further study. Parker and coworker[12] have recommended using only one plasma concentration value for monitoring aminoglycoside by collecting the blood at six hours post-infusion. In this study, we report the mean value of this parameter as 6.79 mg per liter and found no significant difference between both recommended daily dosages.

The correlation between the six hours post-infusion plasma concentration and the area under curve was studied because we wanted to use plasma concentration instead of the area under curve for monitoring Amikacin dosage. The result of this study showed a highly significant correlation using the coefficient of determination so that we could simulate the linear equation for the area under the curve (Table 3).

Furthermore, the study was simulated using the area under the curve and the six hours post-infusion plasma concentration values as the baseline parameters. Clinical correlates of the different values of the area under the curve and six hours post-infusion plasma concentration for monitoring recommendation will be reported further.

CONCLUSION

In this study, we report the mean area under the curve value and six hours post-infusion plasma concentration. The area under the curve needs two plasma samples but the six hours post-infusion plasma concentration needs only one blood sample. The correlation of both parameters will decrease the procedure for the therapeutic monitoring of Amikacin. The result of this report will be further used as a basic parameter for determining the clinical adverse outcome of the once daily dosage regimen of Amikacin.

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