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Gentamicin Dosage Regimens in Thai Cancer Patients(ขนาดและความถี่ในการให้ยา Gentamicin ในผู้ป่วยมะเร็งชาวไทย)

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ORIGINAL ARTICLE

Gentamicin Dosage Regimens in Thai Cancer Patients

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ABSTRACT

Three dosing nomograms for the estimation of gentamicin dosage were evaluated in 35 patients admitted in the National Cancer Institute of Thailand. The pharmacokinetic parameters of gentamicin were also determined following multiple intramuscular or intravenous injections. The results showed that the 3 dosing methods (Sarubbi and Hull, rule of eights, and USPDI) were not significantly different. As judged by the predicted trough level, they all resulted in a large proportion of patients with potentially toxic or subtherapeutic concentrations. Desired trough concentrations were attained in the majority of patients when the dosing intervals were individually calculated based on their half-lives, with the usual dose chosen at 1.35 mg/kg, or in all patients when individualized method was used for determining dosage requirement. These may, in part, be attributable to the fact that wide interpatient variations in gentamicin distribution and elimination were evident. The patients' half-lives ranged from 1.2 to 6.4 hours, in normal renal function patients and the volumes of distribution ranged from 0.09 to 0.50 L/kg, with the mean of 0.25 L/kg. These results, therefore, emphasize the need to measure serum concentrations and consequently make and necessary dosage adjustment, at least in certain cancer populations, to ensure therapeutic levels (Th. J. Pharm. Sci., Vol. 13 No. 4, 365-372 (1988))

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Introduction

Aminoglycosides are commonly used to treat patients with serious gramnegative bacterial infections (1-2). However, their use has often been limited by the occurrence of nephrotoxicity and ototoxicity (2). Although the relationship between serum aminoglycoside concentration and its efficacy or toxicity has rather been established, there has been an increasing concern with its use as the variability in serum levels, resulting from the routine use of recommended dosage regimens is often apparent (3-4). Altered renal function and body temperature, lean body mass, and age have been reported to affect its serum levels. Several standard formulas and nomograms incorporating these factors have been developed to dose patients and to predict serum levels (5-7). A great deal of attention has also been paid to the estimation of individual patients' pharmacokinetic values for the purpose of optimizing dosage regimens. One of the individualized methods commonly used, the Sawchuck and Zaske (8-9), has been implemented frequently for providing aminoglycoside dosing services. This method, however, requires a minimum of 3 serum drug levels during postinfusion period. Considering the economic constraints, especially for most cancer patients admitted in the National Cancer Institute in Thailand, and the possibility of these patients being treated with an aminoglycoside, mostly with gentamicin, and the risks associated with its use, it seems valuable to evaluate systematically the published dosing nomograms of gentamicin in Thai patients.

Thus, this paper was aimed to report 1) the suitability of commonly used dosing nomograms and the likely usual dose range of gentamicin for Thai patients, and 2) the estimates of its pharmacokinetic parameters.

Material and Methods

Patients Thirty-five cancer patients of the surgical or medical services hospitalized at the National Cancer Institute, Bangkok, were studied. They were treated with gentamicin for genito-urinary tract, respiratory tract, or soft tissue infection, or for post- or pre-operative prophylaxis. Some patients also received other medications, such as co-trimoxazole and penicillins during therapy. The patients's ages ranged from 26 to 75 years, with a mean of 53 years. The patients' renal functions were determined by obtaining serum creatinine 1-2 days prior to the initiation of therapy and periodically during therapy.

Procedure Each patient received gentamicin dose of 40, 60 or 80 mg for every 8 hours either by intramuscular injection or 1-hour intravenous infusion for 3-12 days. At least 2 days of administration was allowed for serum concentration to reach a steady-state. Three serum samples were then obtained, with the first two samples were at 5 and 8 hours after dosing or at the end of the infusion, and the last sample was at 1 hour after the next IM dose or at the end of infusion of the following dose. All samples were stored frozen until assayed for gentamicin activity by the microbiological method. The well-agar diffusion method of Giamanellou et al (10) was followed with some modifications: *Klebsiella* spp. (β-lactamase producing strain) and antibiotic medium no. 11 plus 5% agar were used instead of *B. subtilis* or *S. epidermidis,* and Muller-Hinton agar, respectively. The standard curves were usually performed at serum levels of 0.5-16.0 ug/ml, with the coefficients of variation for inter-day and day-day of less than 10%. This method could be employed to detect the gentamicin level in the presence of penicillins without the use of penicillinase, and the detection limit of this method is as low as 0.1 μg/ml.

Calculation Pharmacokinetic parameters were obtained by assuming that the drug had a complete and fast absorption. Half-lives were estimated from the first two data points. Based on the superposition theory, the areas under the curve (AUC) during dosing interval (8 hours) were obtained using 4 data points, with the last sample served as both a predose level and a minimum serum level (serum level at 8 hours after dosing). Since the AUC during a dosing interval obtained following a multiple-dose study is equal to AUC from time zero to infinity after a single dose for a drug with linear kinetics (11), the total body clearance (CL) was then calculated using equation 1. The volume of distribution (Vd) was also determined (equation 2).

NEW PIPRACIL* IV IM

Piperacillin Sodium/Lederle

Organisms	single agents							combinations			
	PIPRACIL	cephalothin	cefoxitin	cefotaxime	tobramycin	ticarcillin	clindamycin	moxalactam	gentamicin + clindamycin	tobramycin + clindamycin	gentamicin + metronidazole
Gram-negative											
Acinetobacter spp.	■					■					
Citrobacter spp.	■			■	■				■	■	■
Enterobacter spp.	■			■	■	■		■	■	■	■
E. coli	■	■	■	■	■	■		■	■	■	■
H. influenzae	■	■	■	■		■		■			
Klebsiella pneumoniae	■	■	■	■	■			■	■	■	■
N. gonorrhoeae	■		■	■		■		■			
N. meningitidis	■					■		■			
Proteus (indole +) spp.	■		■	■	■	■		■	■	■	■
Proteus mirabilis	■	■	■	■	■	■		■	■	■	■
Pseudomonas aeruginosa	■			†	■	■		†	■	■	■
Pseudomonas spp.	■				‡	■					
Serratia marcescens	■			■	■			■	■	■	■
Morganella	■		■	■	■	■		■	■	■	■
Salmonella spp.	■	■		■		■		■	■		■
Shigella	■	■		■				■	■		■
Gram-positive											
Enterococci (incl. s. faecalis)	■					■					
Staphylococcus aureus		■	■	■	■		■	■	■	■	■
Staphylococcus epidermidis		■	■	■	■		■	■	■	■	■
Streptococcus (beta-hemolytic)	■	■	■	■		■	■	■	■	■	■
Streptococcus pneumoniae	■	■	■	■		■	■	■	■	■	■
Streptococcus pyogenes	■	■	■	■		■	■	■	■	■	■
Streptococcus viridans	■	■	■	■		■	■	■	■	■	■
Streptococcus spp.	■	■	■	■		■	■	■	■	■	■
Anaerobes											
Bacteroides fragilis	■		■			■	■	■	■	■	■
Bacteroides spp.	■		■	■		■	■	■	■	■	■
Clostridium difficile[a]	■					■					■
Clostridium spp.	■		■	■				■			■
Eubacterium spp.	■					■	■	■	■	■	■
Fusobacterium spp.	■					■	■	■	■	■	■
Peptococcus spp.	■		■	■		■	■	■	■	■	■
Peptostreptococcus spp.	■		■	■		■	■	■	■	■	■
Veillonella spp.	■					■		■			■

(Data based on PDR,® 35th Edition, 1981 and cefotaxime and moxalactam package inserts).

The aminoglycosides, cephalosporins and clindamycin are more active against beta-lactamase-producing staphylococci. In vitro PIPRACIL is inactivated by staphylococcal beta-lactamases and beta-lactamases produced by gram-negative bacteria. However, it is active against beta-lactamase-producing gonococci.

[a]PIPRACIL has been shown to be active *in vitro* against these organisms; however, clinical efficacy has not yet been established.

†Cefotaxime and moxalactam are active against some strains of *Pseudomonas aeruginosa*.

‡Although not reported in PDR,® 35th Edition, 1981 *in vitro* activity against *Pseudomonas* sp has been recognized.

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$$CL = \frac{\text{Dose given}}{AUC} \text{ during that interval} \quad \text{.....1)}$$

$$Vd = CL/k, \text{ where } k = \text{slope of the terminal phase} \quad \text{.....2)}$$

Gentamicin dosage regimens were determined for all 35 patients using 3 nomogram methods: Sarubbi and Hull (12), rule of eights (13), and USPDI recommended method (14). Each dosing method was used as follows:

Sarubbi and Hull Method: The published dosing chart was used to determine a maintenance dose for each patient, based on the minimum loading dose of 1.5 mg/kg (the recommended usual dose range is 1.5-2.0 mg/kg). According to this dosing chart, doses can be administered every 8 hours in all patients.

Rule of eights: Dose of 1.35 mg/kg administered at variable intervals, depending on serum creatinine values was used for the calculation in this evaluation study. The dosage interval was every 8 hours for those patients with normal serum creatinine level (< 1.4 mg/dL), 12 hours for those with serum creatinine level ranging between 1.5 and 1.8 mg/dL, and 18 hours for those with the level of more than or equal to 1.8 mg/dL.

USPDI: Maintenance dose (MD) in mg given for every 8 hours was calculated by

$$MD = \frac{\text{patient's weight (kg)} \times \text{usual dose (mg/kg)}}{\text{patient's serum creatinine level (mg/dL)}}$$

where the usual dose = 1.35 mg/kg

Individualization of dosage regimens using Chiou's method (15) was also examined. The maintenance dose (mg/kg) and dosing interval (T, hour) following an intravenous infusion were determined as in equations 3 and 4, respectively.

$$T = 1/k \, (\ln Cmax/Cmin) + t' \quad \text{.....3)}$$

$$MD = ((Vd)kt'(Cmax + Cmin)/2) + Vd(Cmax - Cmin) \quad \text{.....4)}$$

where Cmax = desired maximum serum level = 7 μg/ml

Cmin = desired minimum serum level = 0.7 μg/ml

t' = infusion time = 1 hour

For all methods used, ideal body weight (IBW) as given in equations 5 and 6 was employed for patients having the differences between actual body weight (BW) and IBW of more than 15%. For patients having height of less than 5 feet, 45 kg for female or 50 kg for male was considered as IBW.

$$\text{IBW (female, kg)} = 45 + (2.3 \times \text{inches over 5 feet}) \quad \text{.....5)}$$

$$\text{IBW (male, kg)} = 50 + (2.3 \times \text{inches over 5 feet}) \quad \text{.....6)}$$

Results and Discussion

Table 1 summerizes clinical data and the estimates of gentamicin pharmacokinetic parameters. The trough level in one patient was too low to be detected, so that his half-life could not be obtained. Due to mishaps in handling samples, some samples could not be analysed, and as a result, the AUC as well as CL and Vd could be estimated only in 29 patients. Out of 35 patients participated in this study, only 7 patients had the differences between BW and IBW of greater than 15%. The values of CL and Vd shown were calculated on an ideal weight basis. As it is known that gentamicin distribution is solely limited to the extracellular fluid, the average value of volume of distribution of 0.025 L/kg obtained in this study is consistent with its pharmacokinetic behaviour. It is interesting to note that although the parameters obtained in the present multipledose study are merely approximated, their average values are all very close to those reported in earlier studies (9,16). This may also indicate that the genetic differences is probably not a problem with gentamicin. The wide variability of the parameters demonstrated even in the patients with normal creatinine levels, also agreeing with previous reports (17-18), confirms that there is also a need for dosage individualization for Thai patients.

Table 1 Clinical Data and Pharmacokinetic Parameters of Gentamicin Following Normal Dosage Regimens of 40, 60 or 80 mg Every 8 Hours

	Female	Male	Total
Age (years)	54.6 ± 13.6 (20)	51.5 ± 14.0 (15)	53.3 ± 13.5 (35)
Serum Creatinine (mg/dL)	1.18 ± 0.44 (20)	1.26 ± 0.22 (15)	1.21 ± 0.36 (35)
Creatinine CL (ml/min)	68.98 ± 23.51 (20)	72.58 ± 17.41 (15)	70.52 ± 20.60 (35)
Trough Level (μg/ml)	2.01 ± 2.33 (20)	2.06 ± 1.30 (14)	2.04 ± 1.92 (34)
Peak Level (μg/ml)	6.29 ± 3.23 (20)	7.15 ± 3.21 (15)	6.66 ± 3.16 (35)
Half-life (hour)	3.38 ± 2.04 (19)	4.00 ± 2.94 (12)	3.62 ± 2.36 (31)
AUC ($\mu g/ml.hour^{-1}$)	33.61 ± 24.38 (18)	37.78 ± 12.41 (11)	35.19 ± 20.14 (29)
CL (L/hour/kg)	0.066 ± 0.039 (18)	0.045 ± 0.022 (11)	0.058 ± 0.034 (29)
Vd (L/kg)	0.26 ± 0.11 (18)	0.23 ± 0.13 (11)	0.25 ± 0.11 (29)

Values in parentheses are number of patients.

Table 2 shows the gentamicin dosage requirement estimated by using 3 different dosage nomograms for 35 patients. If can be seen that the average dose calculated by the rule of eights method was somewhat higher, and the dosing intervals were longer, in some patients, than that obtained by the other methods. However, the predicted minimum serum levels obtained by all methods were comparable, suggesting that these 3 methods were clinically equivalent. Closer examination revealed that with both Sarubbi and Hull, and USPDI methods, 8 patients (out of 34 patients) had predicted trough levels of more than 2 μg/ml, while with the rule of eights, 7 patients had the levels of more than 2 μg/ml and 2 patients had the levels of less than 0.1 μg/ml. Since the trough level of greater than 2 μg/ml has been reported to be often associated with ototoxicity and renal toxicity (4,19), these results may suggest that the 3 dosing methods are probably unsatisfactory for use in Thai patients. However, when the usual doses of lower than those recommended, i.e., 1.35 mg/kg for the Surubbi and Hull, and 1 mg/kg for the USPDI and for the rule of eights, were used for the calculation, there were fewer patients with the gentamicin levels of greater than 2 μg/ml, but there were also more cases having the levels of less than 0.1 μg/ml (Table 3).

Table 2 Dosage Regimens and Predicted Trough Levels Obtained by Using Three Dosing methods

Dosing Method	Dose (mg)	Interval (hour)	Predicted Trough Level (μg/ml)
Sarubbi and Hull	56.36 ± 13.35 (35)	8 (35)	1.35 ± 0.93 (34)
USPDI	59.53 ± 17.74 (35)	8 (35)	1.34 ± 0.88 (34)
Rule of Eights	66.86 ± 9.47 (35)	8 (25) 12(9) 18(1)	1.34 ± 1.03 (34)

Values in parenthese are number of patients

Table 3 Results Obtained with Reduced Usual Dose for Three Dosing Methods

Dosing Method	Usual Dose (mg/kg)	Predicted Trough Level (μg/ml)	Number of Patients Having Predicted Trough Level of	
			> 2 μg/ml	< 0.1 μg/ml
Sarubbi and Hull	1.35	1.21 ± 0.84	4	1
USPDI	1.0	0.99 ± 0.65	3	1
Rule of Eights	1.0	0.99 ± 0.77	3	2

The apparently poor performance of these 3 dosing methods could probably be partly explained as follows: With the rule of eights, serum creatinine concentrations are used to estimate dosing intervals, while the doses are being fixed. In contrast, in USPDI method the creatinine levels are used to calculate gentamicin doses, with the fixed interval. It has long been recognised that serum creatinine alone could not be employed accurately in predicting renal function and consequently gentamicin elimination since its values are also affected by body mass, age and sex as well. To account for these factors, the dosing methods using creatinine clearance are usually prefered (20), as in the case of the Sarubbi and Hull method. However, there is also a poor correlation obtained between creatinine clearance and gentamicin half-life ($r = 0.5190$) or between the clearances of creatinine and gentamicin ($r = 0.4239$) in the present study.

In evaluating the suitability of the 3 dosing methods, the minimum level was used in this study since it is less affected by routes of administration than the maximum level and it is rather reliable in predicting toxicity of gentamicin. By assuming linear kinetics for gentamicin, the predicted trough level could readily be calculated as it would be altered proportionately to the dose given. Due to intersubject variations of absorption process, the concentration obtained after 1 hour of intramuscular administration may not be the peak level. Thus, the maximum serum level obtained following intramuscular administration as in this study could not be used accurately to predict the toxic potential, although the peak of more than 10 μg/ml may be a suggestion of toxicity (3).

Since a plasma half-life could be used as a better guide for the estimation of a dosing interval as compared to serum creatinine or creatinine clearance and since it can be obtained by using 2 serum levels during the terminal phase, an alternative method for gentamicin dosing was then proposed. Based

on the present result, the maintenance dose was chosen at 1.35 mg/kg and the dosing interval was determined by equation 3, rounding off to the closest convenient interval, e.g., 6, 8, 12 hours, etc. With the Cmax and Cmin assumed to be 10 and 0.6 μg/ml, respectively, the gentamicin dosage regimens and the predicted trough levels were determined (Table 4). It was found that the predicted minimum levels of 34 patients were within 0.3-2 μg/ml, except in one case, where a little higher than 2 μg/ml was obtained. Thus, based on this proposed method only 2 serum levels are required individually to estimate their own half-lives and accordingly the dosing intervals. The usual dose of gentamicin for Thai patients may range from 1 to 1.8 mg/kg. These regimens would provide, to this group of patients, the average trough levels of 0.5-1.0 μg/ml, with only 2 patients having the levels exceeding 2 μg/ml. It is of interest to note, however, that this method could be employed satisfactorily only if the 2 levels are obtained at an appropriate time interval during post distribution phase, and with the accurate and sensitive assay.

Table 4 Results Obtained by the Proposed Method with the Usual Dose of 1.35 mg/kg

Dosing Interval (hour)	No.of Subjects	Half-life (hour)	Predicted Trough Level (μg/ml)
6	1	1.16	0.31
8	13	1.73-2.56	0.87 ± 0.51
12	9	2.60-3.72	0.75 ± 0.52
18	3	4.48-5.13	0.51 ± 0.10
24	3	5.70-6.45	0.68 ± 0.41
36	1	9.62	0.35
48	1	12.33	0.53

It is generally accepted that for drugs exhibiting high pharmacokinetic variability, the individualization of dosage regimens is the best dosing method, though it is rater costly. In Chiou's dosing method, both maintenance doses and dosing intervals are variable depending on the estimated half-lives and Vd's. As expected, there were wide variations of maintenance doses (0.64-3.10 mg/kg, mean = 1.8 mg/kg) and dosing intervals (8-24 hours) obtained even in patients with normal serum creatinine or creatinine clearance. With these regimens, all predicted serum levels were within 2 μg/ml. Although this method is intended for dosage determinations following intravenous administration, it could also be used to approximate the dosage regimens following intramuscular administration by assuming a fast and complete absorption.

In summary, the present study indicates that the 3 published dosing methods may be used for the initial estimation of gentamicin dosage requirement in Thai cancer patients. Subsequently, peak and trough concentrations should then be measured for further dosage adjustment. In addition, the dosage regimens for an individual patient may also be better estimated by obtaining at least 2 serum samples, at an appropriate time interval, for the determination of dosing intervals, with the usual dose set at about 1.35 mg/kg IBW. The implications of these results, however, have yet remained to be proven for a larger population size.

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650/7ก ละไม
650/0ก Gentamicin

ขนาดและความถี่ในการให้ยา Gentamicin ในผู้ป่วยมะเร็งชาวไทย

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บทคัดย่อ

ได้ศึกษาเปรียบเทียบวิธีการคิดขนาดและความถี่ในการให้ยา Gentamicin 3 วิธี (Sarubbi and Hull, rule of eights และ USP DI) ในผู้ป่วยมะเร็งจำนวน 35 คน ที่รักษาตัวในสถาบันมะเร็งแห่งชาติ พบว่าขนาดและช่วงเวลาที่คำนวณได้จาก 3 วิธีมีความแตกต่างกันเล็กน้อย โดยการคาดคะเนระดับยาในเลือดต่ำสุด (trough level) พบว่าทั้ง 3 วิธีจะให้ระดับต่ำสุดที่สูงเกิน 2 µg/ml ซึ่งอาจก่อให้เกิดอันตราย หรือต่ำเกินไปทำให้ไม่ได้ผลในการรักษาในผู้ป่วยหลายคน เมื่อทำการคิดขนาด และช่วงเวลาในการให้ยาโดยวิธีคำนวณช่วงเวลา (dosing interval) จากค่ากึ่งชีวิต (half-life) ของ Gentamicin ของผู้ป่วยแต่ละคน และกำหนดขนาดที่ให้เป็น 1.35 mg/kg พบว่าระดับยาต่ำสุดอยู่ในเกณฑ์ที่น่าพอใจในผู้ป่วยส่วนใหญ่ และเมื่อคิดขนาดและความถี่ในการให้ยาโดยวิธีปรับทั้งขนาดและช่วงเวลาให้เหมาะสมกับคนไข้เป็นราย ๆ (individualized method) พบว่าคนไข้ทั้งหมดมีระดับยาต่ำสุดเหมาะสม เหตุผลที่วิธีการคิดขนาดและความถี่ในการให้ยาโดย 3 วิธีดังกล่าวข้างต้นไม่ได้ผลดีเท่าที่ควร อาจเป็นเพราะค่าทางเภสัชจลนศาสตร์ (pharmacokinetic parameter) มีความแตกต่างกันมากในระหว่างคนไข้แต่ละคน ค่ากึ่งชีวิตของ Gentamicin อยู่ระหว่าง 1.2 และ 6.4 ชม. ในคนไข้ที่มีการทำงานของไตปกติ และค่าปริมาตรการกระจายตัวของยา (volume of distribution) มีตั้งแต่ 0.09 ถึง 0.5 L/kg ดังนั้นผลการศึกษาครั้งนี้ชี้ให้เห็นความจำเป็นที่จะต้องวัดระดับยา Gentamicin ในเลือดในผู้ป่วยชาวไทย (ไทยเภสัชสาร ปีที่ 13 (4) : หน้า 365-372 (2531))

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