CHAPTER IV

RESULTS AND DISCUSSION

I. Serum Gentamicin Levels and the Therapeutic Range

Eighty-two admitted patients who met the criteria of this study were analyzed. Table 1 showed the characteristics of patients, table 2 showed the dosage regimen administered to patients according to the traditional method and their corresponding measured serum gentamicin levels. Also included in table 2 was the result of treatment. The dosage regimen in forty-four patients were adjusted using pharmacokinetic method.

The clinical results of thirty-three patients were followed up. The patient was indicated as showing positive result if he or she had available normal value of temperature, WBC, pulse, culture sensitivity within 48 hours after the drug was administered or was cured without changing of the drug. Thirty-two patients showed sign of improvement while one patient showed negative improvement.

Physicians in Police General Hospital usually do not apply pharmacokinetics for gentamicin dosage regimen calculation. Their traditional methods were usually started with gentamicin maintenance dose and the normal dosage regimen was 60 or 80 mg/dose and was given for every 8 hours.The drug was either administered by IM, IV infusion or IV push, the number of patients treated by IM,IV infusion and IV push were 49, 27 and 6 respectively.

TABLE 1 Characteristics of Patients

Patient Number	Sex	Age (year)	TBW[1] (kg)	IBW[2] (kg)	Height (cm)	Scr[3] (mg/dl)
1	M	29	59	64.72	166	0.82
2	F	70	48	47.34	152	1.03
3	M	47	55*	68.4	170*	0.83
4	F	67	43	48.26	153	1.45
5	M	31	52	69.32	171	0.79
6	M	59	52	58.28	159	1.01
7	M	20	53	62.88	164	0.9
8	M	25	66	61.04	162	0.9
9	F	15	47	50.0	155	0.75
10	M	35	55*	64.72	166*	0.9
11	M	26	59*	69.32	171*	0.82
12	M	30	49	64.72	166	0.81
13	F	16	45	46.42	151	0.94
14	M	33	61	68.4	170	0.85
15	F	75	50	50.1	155	0.8
16	M	40	58	70.24	172	0.95
17	M	19	54	70.24	172	1.07
18	M	42	64	68.4	170*	1.99
19	F	64	47	50.1	155	0.81
20	M	22	62*	73	175*	1.17

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Patient Number	Sex	Age (year)	TBW[1] (kg)	IBW[2] (kg)	Height (cm)	Scr[3] (mg/dl)
21	M	57	42*	50	150*	0.87
22	M	17	62	68.4	170	0.94
23	M	23	56	60.12	161	0.9
24	M	41	38	59.2	160	1.13
25	F	17	45*	63.9	170	0.81
26	M	32	55	61.96	163	0.85
27	F	35	43	48.26	153	0.81
28	F	30	57	50.1	155	0.71
29	F	38	50*	52.86	158	0.67
30	M	19	56	63.8	165	0.89
31	F	40	54	51.94	157	0.78
32	M	19	57	73	175	0.97
33	F	19	40	54.7	160	0.72
34	M	19	46*	62.88	164*	0.77
35	M	27	58*	61.04	162*	0.75
36	M	20	44	59.2	160	1.64
37	M	18	47	51.84	152	0.66
38	M	47	47	54.6	155	0.44
39	M	42	65	65.64	167	0.9
40	M	57	48	58.28	159	1.3
41	F	55	46	56.54	162	0.59
42	M	25	57	50	150	0.9
43	M	27	65	73.92	176	0.9
44	M	33	78	75.76	178	1.26
45	M	26	47	68.4	170	0.99
46	M	24	58	53.68	154	1.06

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Patient Number	Sex	Age (year)	TBW[1] (kg)	IBW[2] (kg)	Height (cm)	Scr[3] (mg/dl)
47	M	52	51	57.36	158	0.97
48	F	23	39	45.5	150	0.68
49	F	63	61	56.54	162	0.82
50	M	28	55	65.64	167	0.82
51	M	21	63	66.56	168	1.15
52	F	54	45	50.1	155	0.72
53	M	25	80	63.8	165	0.93
54	M	27	52	58.28	159	0.9
55	F	30	45	59.3	165	0.4
56	F	62	34	43.66	148	0.54
57	M	20	60	67.48	169	1.02
58	M	21	46	61.04	162	1.37
59	M	15	54	57.36	158	0.99
60	M	32	85	61.04	162	1.3
61	M	23	43*	57.36	158	0.86
62	F	73	38	50.1	155	0.97
63	M	15	43*	52.76	153*	0.01
64	M	33	65	63.8	165	0.81
65	M	23	64	65.64	167	0.93
66	F	16	48	43.66	148	0.94
67	F	22	55	51.94	157	0.74
68	F	23	48	46.42	151	0.78
69	M	43	70	72.08	174	0.9
70	M	56	60*	63.8	165*	0.85
71	F	82	60	40.9	145	1.19
72	M	20	65*	63.8	165*	0.99

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Patient Number	Sex	Age (year)	TBW[1] (kg)	IBW[2] (kg)	Height (cm)	Scr[3] (mg/dl)
73	F	67	55*	45.5	150*	0.85
74	M	33	50	63.8	165	1.06
75	M	30	56	73	175	1.1
76	F	21	35	51.02	156	0.78
77	F	15	42	47.34	152	0.75
78	F	16	55	54.7	160	0.56
79	F	16	45	54.7	160*	0.85
80	F	47	77*	45.5	150*	1.52
81	F	60	50	45.5	150*	0.64
82	M	27	60*	73	175*	0.6
$\bar{X}\pm SD$	M=52 F=30	32.22±17.13	53.58±9.72	58.73±8.79	161.28±7.96	0.92±0.25
(Range)		(15-82)	(34-85)	(40.9-75.76)	(145-178)	(0.04-1.99)

1 TBW = Total Body Weight

2 IBW = Ideal Body Weight

3 Scr = Serum Creatinine

* Measurement with Questionaire or Estimation

Table 2 Dosage regimen and measured serum gentamicin concentration in patients whose gentamicin were given by traditional method

Patient Number	Maintenance Dose (mg)	Interval (hour)	Route[1]	Trough (μg/ml)	Peak[2] (μg/ml)	Result of[3] treatment
1	80	8	IM	0.90	4.37	I
2	60	8	IM	3.93	8.46	I
3	80	8	IV(inf)	2.03	5.50	I
4	60	8	IV(inf)	3.96	8.15	A
5	80	8	IV(inf)	0.41	4.48	A
6	60	8	IV(inf)	1.11	5.44	I
7	80	8	IM	0.53	3.60	I
8	80	8	IM	0.69	3.05	A
9	60	8	IM	0.80	4.37	A
10	80	8	IM	0.55	4.25	I
11	80	8	IM	0.37	3.25	A
12	80	8	IM	0.24	3.64	A
13	60	8	IM	1.39	4.99	I
14	80	8	IM	0.38	3.11	A
15	80	8	IV(inf)	1.47	8.51	I
16	80	8	IV	0.71	3.52	A
17	80	8	IV	0.52	4.16	A
18	40	8	IM	2.02	2.85	A
19	60	8	IM	0.84	2.42	A
20	80	8	IM	0.74	3.13	A
21	60	8	IM(inf)	1.03	4.85	I
22	80	8	IM	0.67	3.72	A
23	80	8	IM	0.64	4.84	I
24	80	8	IM	1.71	6.36	I

Continued .....

Patient Number	Maintenance Dose (mg)	Interval (hour)	Route[1]	Trough (µg/ml)	Peak[2] (µg/ml)	Result of[3] treatment
25	80	8	IV(inf)	0.45	4.89	A
26	80	8	IV(inf)	0.60	5.08	A
27	80	8	IM	1.13	6.60	I
28	80	8	IV push	0.51	HI	-
29	60	8	IV(inf)	0.45	3.04	A
30	80	8	IM	0.92	5.10	I
31	80	12	IV push	0.11	HI(4.52*)	-
32	80	8	IM	0.88	3.82	A
33	60	8	IM	0.90	3.65	-
34	80	8	IM	0.35	3.63	I
35	80	8	IM	0.64	3.72	A
36	80	8	IV(inf)	2.21	7.59	A
37	80	8	IV(inf)	2.23	4.83	A
38	60	8	IV(inf)	0.67	3.58	A
39	80	8	IV(inf)	0.55	5.58	A
40	80	8	IV(inf)	1.74	6.80	I
41	80	8	IM	0.63	4.59	A
42	80	8	IM	0.50	4.41	A
43	80	8	IM	1.11	4.51	I
44	80	8	IV(inf)	0.55	4.33	I
45	80	12	IV push	0.24	HI(4.12)*	-
46	80	8	IM	0.42	3.39	I
47	80	8	IM	1.07	4.97	I
48	80	8	IV push	0.69	HI(6.05)*	-
49	60	8	IM	0.94	4.06	I
50	80	8	IM	0.33	3.05	A

Continued .....

Patient Number	Maintenance Dose (mg)	Interval (hour)	Route[1]	Trough (µg/ml)	Peak[2] (µg/ml)	Result of[3] treatment
51	80	8	IM	0.20	3.62	A
52	80	8	IV(inf)	0.84	5.67	A
53	100	8	IV(inf)	0.49	4.48	N
54	80	8	IM	0.62	4.32	I
55	80	8	IV(inf)	1.53	4.82	I
56	80	8	IV push	0.67	HI(5.21*)	A
57	80	8	IM	0.61	4.44	I
58	80	8	IM	0.70	4.97	A
59	60	8	IM	2.23	4.89	A
60	80	8	IV(inf)	1.79	4.46	-
61	80	8	IM	0.85	4.20	A
62	60	8	IM	4.86	HI	A
63	80	8	IV(inf)	1.94	7.30	I
64	80	8	IM	0.44	3.85	A
65	80	8	IM	0.54	3.22	I
66	80	8	IM	0.97	6.02	I
67	80	8	IM	0.90	5.51	I
68	80	8	IM	0.69	4.34	A
69	80	8	IV(inf)	0.60	3.81	A
70	80	8	IV(inf)	0.67	3.59	A
71	60	8	IM	2.55	6.07	A
72	80	8	IV(inf)	1.39	4.55	I
73	80	8	IV push	1.14	HI(5.02)*	A
74	80	8	IM	0.57	4.10	I
75	80	8	IV(inf)	0.73	4.97	A

Continued .....

Patient Number	Maintenance Dose (mg)	Interval (hour)	Route[1]	Trough (µg/ml)	Peak[2] (µg/ml)	Result of[3] treatment
76	80	8	IM	0.95	7.86	I
77	60	8	IM	0.82	6.80	A
78	80	8	IM	0.61	4.33	A
79	80	8	IM	1.01	5.94	I
80	80	8	IM	8.08	12.52	A
81	80	8	IM	0.95	4.53	I
82	60	8	IV(inf)	1.09	3.59	A

[1] Route IM = Intramuscular (n = 49)

IV(inf) = Intravenous infusion (n = 27)

IV push = Intravenous push (n = 6)

[2] Peak HI = Serum gentamicin concentration > 12 µg/ml

* = Serum gentamicin concentration at one hour after IV push

[3] Result of treatment I = Improved (n = 32)

N = Not Improved (n = 1)

A = Adjust dosage regimen (n = 44)

- = not complete follow up (n = 5)

Table 3A-3E showed percentage of patients versus gentamicin serum concentration and therapeutic range when drug dosage regimen was given according to current traditional practice.

Table 3A showed the result of all 82 patients, table 3B showed the result of patients who has impaired renal function only,table 3C showed the result of patients who received gentamicin by IM only, table 3D showed the result of patients who received gentamicin by IV infusion only while table 3E showed comparison among different methods of administration.

The results obtained indicated that when gentamicin was given according to the physicians traditional dosage regimen, majority of the patients will have subtherapeutic trough concentrations. Patients with impaired renal function showed lower percentage of patients whose both peak and trough concentrations were within the therapeutic range and also showed much lower percentage of patients whose trough concentration only was within subtherapeutic range. At the same time, the percentage of patients with overtherapeutic trough concentration was much higher. Therefore, it is quite obvious that the patients with impaired renal function required a more careful consideration on the suitable dosage regimen administered than the normal patients. The IV infusion method showed a little bit higher percentage of patients whose peak or trough serum gentamicin concentrations were within the therapeutic range as compared to the IM method.

Table 3 Percentage of patients whose serum gentamicin concentrations were within therapeutic,subtherapeutic and overtherapeutic. Gentamicin was given by traditional dosing method

A : all patients were included.

Serum Gentamicin Level[1]		Number of Patients (n=82)	Percentage	Number of patients followed up (n=33)	Number of patients with clinical improvement (n=32)	Percentage of improvement
Peak	Trough					
T	T	25	30.49	21	21	100
T	S	30	36.58	9	8	88.89
T	O	5	6.10	1	1	100
S	T	2	2.44	-	-	-
S	S	12	14.63	2	2	100
O	O	2	2.44	-	-	-
O	S	5	6.10	-	-	-
O	T	1	1.22	-	-	-

[1] Serum Gentamicin Level within T = Therapeutic range

S = Subtherapeutic range

O = Overtherapeutic range

B : Patients with impaired renal function (Scr $\geq$ 1.10)

Serum Gentamicin Level		Number of Patients (n=13)	Percentage	Number of patients followed up (n=4)	Number of patients with clinical improvement (n=4)	Percentage of improvement
Peak	trough					
T	T	3	23.08	2	2	100
T	S	4	30.77	1	1	100
T	O	3	23.08	1	1	100
S	T	1	7.69	-	-	-
S	S	1	7.69	-	-	-
O	O	1	7.69	-	-	-

C : Patients who received gentamicin by IM only.

Serum Gentamicin Level		Number of Patients (n=49)	Percentage	Number of patients followed up (n=23)	Number of patients with clinical improvement (n=23)	Percentage of improvement
Peak	trough					
T	T	16	32.65	13	13	100
T	S	20	40.82	7	7	100
T	O	2	4.08	1	1	100
S	T	1	2.04	-	-	-
S	S	8	16.33	2	2	100
O	O	2	4.08	-	-	-

D : Patients who received gentamicin by IV infusion

Serum Gentamicin Level		Number of Patients (n=27)	Percentage	Number of Patients followed up (n=10)	Number of patients with clinical improvement (n=9)	Percentage of improvement
Peak	trough					
T	T	9	33.33	8	8	100
T	S	10	37.09	2	1	50
T	O	3	11.11	-	-	-
S	T	1	3.70	-	-	-
S	S	4	14.82	-	-	-

Table 3E Comparison among different groups of patients, the percentage of patients whose serum gentamicin were within therapeutic, subtherapeutic and overtherapeutic range .

Serum gentamicin concentration		Percentage of patients			
		ALL patients	Impaired renal	IM only	IV(infusion) only
Both peak and trough	T	30.49	23.08	32.65	33.33
Peak	T	73.17	76.93	77.55	81.53
	O	9.76	7.69	4.08	0
	S	17.07	15.38	18.37	18.52
Trough	T	34.15	30.77	34.69	37.03
	O	8.54	30.77	8.16	11.11
	S	57.31	38.46	57.15	51.91

Also showed in table 3A, 3B, 3C and 3D were the percentage of patients who showed improvement on the treatment. However, since the number of patients whose clinical result had been followed up were too little (sometimes, there were only one or two patients in a group), any serious conclusion on the relationship between serum gentamicin concentration and the clinical outcome could not be made. Any way, when the trough concentration was in the subtherapeutic range the percentage of patients with clinical improvement showed the tendency to be lower.

Forty-four patients' dosage regimen were adjusted using pharmacokinetic methods and the drug was given by IV infusion. Table 4 showed the dosage regimen given, predicted and measured serum gentamicin concentrations. Also included was result of the treatment, thirty-five patients were follow up for their clinical results. Thirty-three patients showed sign of improvement, two patients showed negative improvement. Six patients needed readjustment of the dosage regimen for the second time.

Table 5A-5D showed the percentage of patients whose serum gentamicin concentration were within therapeutic, subtherapeutic and overtherapeutic range after gentamicin was given with individual pharmacokinetic calculated dosage regimen using IV infusion method.

Table 5A showed the result of all 44 patients, either initally received gentamicin by IM,IV infusion or IV push, table 5B showed the result of 25 patients who

Table 4 Dosage Regimen, Predicted and Measured Serum Gentamicin Concentrations in patients whose dosage regimen were adjusted by individual pharmacokinetic (Sawchuk-Zaske) method and given by IV infusion

Patient Number	Number of Adjustment	Maintenance Dose(mg)	Interval (hour)	Predicted		Measured		Result of[1] treatment
				Trough (μg/ml)	Peak (μg/ml)	Trough (μg/ml)	Peak (μg/ml)	
4	1	60	12	1.88	6.18	3.59	6.02	I
5	1	100	6	0.90	5.93	1.13	8.65	I
8	1	90	8	1.06	5.90	0.35	5.20	N
9	1	85	8	1.05	7.44	1.36	7.35	I
11	1	90	6	0.99	6.24	1.18	6.57	I
12	1	90	6	0.69	6.94	2.35	7.77	I
14	1	90	6	1.03	6.12	0.90	6.05	-
16	1	100	8	0.77	4.30	1.32	8.16	I
17	1	95	6	1.03	5.30	0.48	5.37	I
18	1	80	24	1.90	6.59	0.70	5.44	I
19	1	70	12	0.99	6.41	0.47	3.39	A
	2	90	8	1.47	5.66	1.53	12.96	I
20	1	80	8	1.07	5.66	0.63	4.78	I
22	1	90	8	0.82	5.95	0.48	3.34	-
25	1	90	6	0.89	5.83	0.73	5.19	-
26	1	80	6	1.02	5.44	1.16	6.36	I
29	1	100	6	1.22	5.48	0.82	8.02	I
32	1	80	8	1.12	6.11	0.74	5.05	I
35	1	80	6	1.39	6.18	0.75	4.94	I
36	1	60	8	1.47	5.52	1.84	7.73	I
37	1	100	12	1.30	4.63	1.29	3.54	A

Continued.....

Patient Number	Number of Adjustment	Maintenance Dose(mg)	Interval (hour)	Predicted		Measured		Result of[1] treatment
				Trough (μg/ml)	Peak (μg/ml)	Trough (μg/ml)	Peak (μg/ml)	
	2	120	12	1.44	4.14	0.96	6.94	I
38	1	100	6	1.75	6.53	1.91	7.53	I
39	1	100	6	1.20	7.41	2.33	7.91	A
	2	80	6	1.58	6.08	1.79	7.66	I
41	1	80	6	1.38	7.38	0.37	3.95	I
42	1	100	6	1.13	7.17	1.11	16.53	I
48	1	80	8	0.78	7.98	1.54	7.79	-
50	1	100	6	1.12	7.37	0.79	5.21	N
51	1	100	6	0.51	5.88	1.00	6.21	I
52	1	100	8	0.89	6.96	1.24	6.12	I
56	1	80	8	1.03	9.31	0.79	7.64	-
58	2	80	8	1.41	7.42	0.30	5.13	I
59	1	80	12	1.80	7.22	0.60	9.81	I
61	1	80	8	1.24	7.83	1.02	4.07	I
62	1	40	12	-	-	8.82	13.11	A
	2	60	48	1.46	8.10	4.39	8.24	I
64	1	100	6	1.00	6.30	1.02	6.46	I
68	1	80	8	1.54	7.32	0.67	6.26	I
69	1	100	6	1.21	5.16	1.47	4.16	I
70	1	100	6	1.48	5.06	2.31	6.02	A
	2	80	6	1.60	4.59	1.79	4.71	I

Continued .....

Patient Number	Number of Adjustment	Maintenance Dose(mg)	Interval (hour)	Predicted		Measured		Result of[1] treatment
				Trough (µg/ml)	Peak (µg/ml)	Trough (µg/ml)	Peak (µg/ml)	
71	1	80	12	1.34	6.21	1.74	5.67	I
73	1	80	8	1.32	6.50	1.54	5.32	-
75	1	80	6	1.19	5.37	2.08	5.74	-
77	1	80	6	1.31	7.88	1.29	0.63	I
78	1	80	6	1.18	6.21	1.15	5.15	I
80	1	80	24	1.01	4.90	1.89	5.52	-
82	1	100	8	1.62	5.80	0.65	6.03	A
	2	100	6	1.12	6.43	0.98	5.96	-

[1] Result of treatment I = Improved (n = 33)

N = Not Improved (n = 2)

A = Adjust dosage regimen (n = 6)

- = not complete follow up (n = 9)

Table 5 Percentage of Patients whose Serum Gentamicin concentration were within therapeutic, subtherapeutic and overtherapeutic range. Gentamicin was given by IV infusion using Individual Pharmacokinetic (Sawchuk-Zaske)Method

A : All patients, either initially received gentamicin by IM, IV infusion or IV push.

Serum Gentamicin Level		Number of Patients (n=44)	Percentage	Number of patients followed up (n=33)	Number of patients with clinical Improvement (n=33)	Percentage of Improvement
Peak	Trough					
T	T	23	52.27	17	17	100
T	S	13	29.54	11	9	81.82
T	O	3	6.82	3	3	100
O	T	3	6.82	3	3	100
S	S	1	2.27	-	-	-
O	S	1	2.27	1	1	100

B : Patients who initially received gentamicin by IM only.

Serum Gentamicin Level		Number of Patients (n=25)	Percentage	Number of patients followed up (n=22)	Number of patients with clinical Improvement (n=20)	Percentage of Improvement
Peak	trough					
T	T	9	36	7	7	100
T	S	9	36	9	7	77.78
T	O	2	8	2	2	100
O	T	3	12	3	3	100
S	S	1	4	-	-	-
O	S	1	4	1	1	100

C : Patients who initially received gentamicin by IV infusion only.

Serum Gentamicin Level		Number of Patients (n=16)	Percentage	Number of patients followed up (n=13)	Number of patients with clinical Improvement (n=13)	Percentage of Improvement
Peak	trough					
T	T	12	75	10	10	100
T	S	3	18.75	2	2	100
T	O	1	6.25	1	1	100

D : Patients who initially received gentamicin by IV push only.

Serum Gentamicin Level		Number of Patients (n=3)	Percentage	Number of patients follow up (n=0)	Number of patients with clinical Improvement (n=0)	Percentage of Improvement
Peak	trough					
T	T	2	66.67	-	-	-
T	S	1	33.33	-	-	-

initially received gentamicin by IM only, table 5C showed the result of 16 patients who initially received gentamicin by IV infusion only and table 5D showed the result of 3 patients who initially received gentamicin by IV push only.

The result showed that patients who initially received gentamicin by IV infusion method will give a better prediction when the adjustment of the dosage regimen was required as seen from the higher percentage of patients whose peak and/or trough concentrations were within the therapeutic range when compare with patients who initially received gentamicin by IM or IV push.

The clinical outcome showed that the percentage of improvement was lower when the trough concentration was in the subtherapeutic range.

II Comparison of Percentage between Traditional and Pharmacokinetic Method of Patients whose Serum Gentamicin were within Therapeutic Range.

Table 6A-6C and figure 1A-1C showed comparison of the percentage of patients whose serum gentamicin were within therapeutic, subtherapeutic and overtherapeutic range after gentamicin was administered with pharmacokinetic calculated dosage regimen. Also included in the table was the effect of initial route of administration, IM or IV infusion. Table 6A and figure 1A showed the result obtained when both peak and trough were considered, table 6B and figure 1B showed the result

Table 6 Comparison between traditional and pharmacokinetic method, Percentage of Patients whose serum gentamicin were within therapeutic, subtherapeutic and overtherapeutic range.

A : Both peak and trough were considered

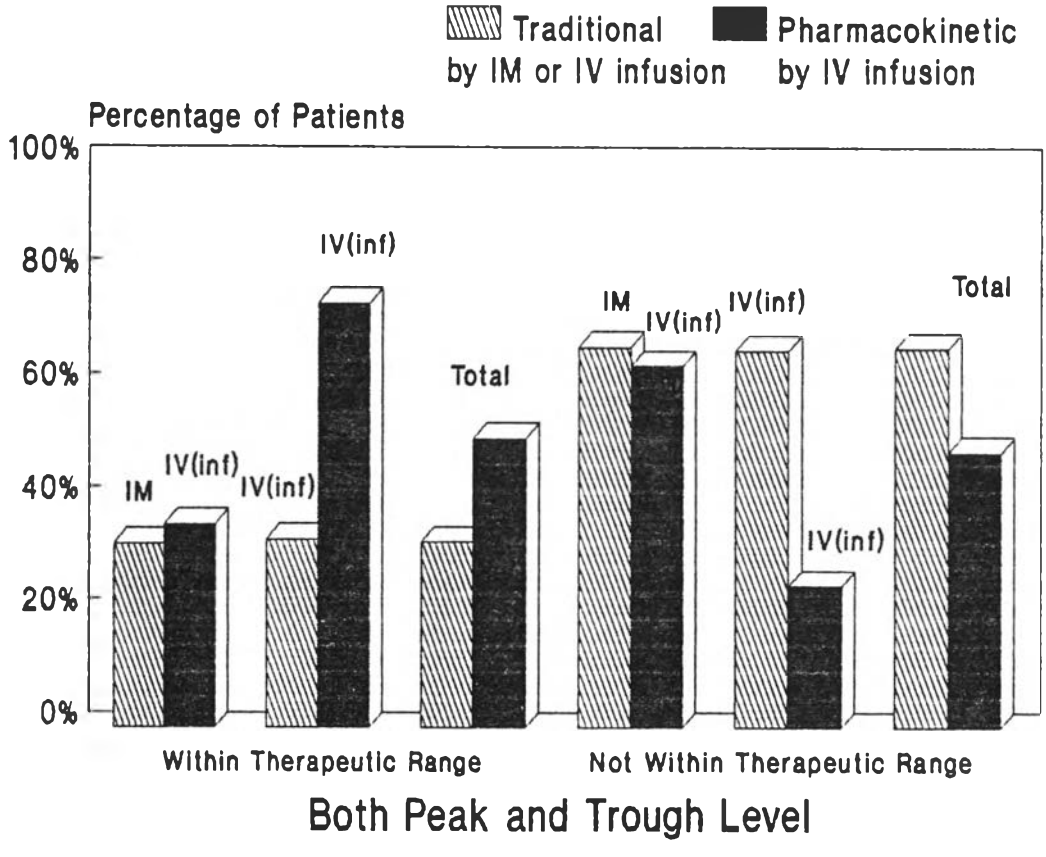
Both peak and trough	Percentage of Patients (N)					
	Initial dosage regimen (Traditional method)			After dosage adjustment (Pharmacokinetic method)		
	IM	IV(inf)	Total	IV(inf)	IV(inf)	Total
within therapeutic	32.65(16)	33.33(9)	32.89(25)	36(9)	75(12)	51.22(21)
not within therapeutic	67.35(33)	66.67(18)	67.11(51)	64(16)	25(4)	48.78(20)

B : Peak only was considered

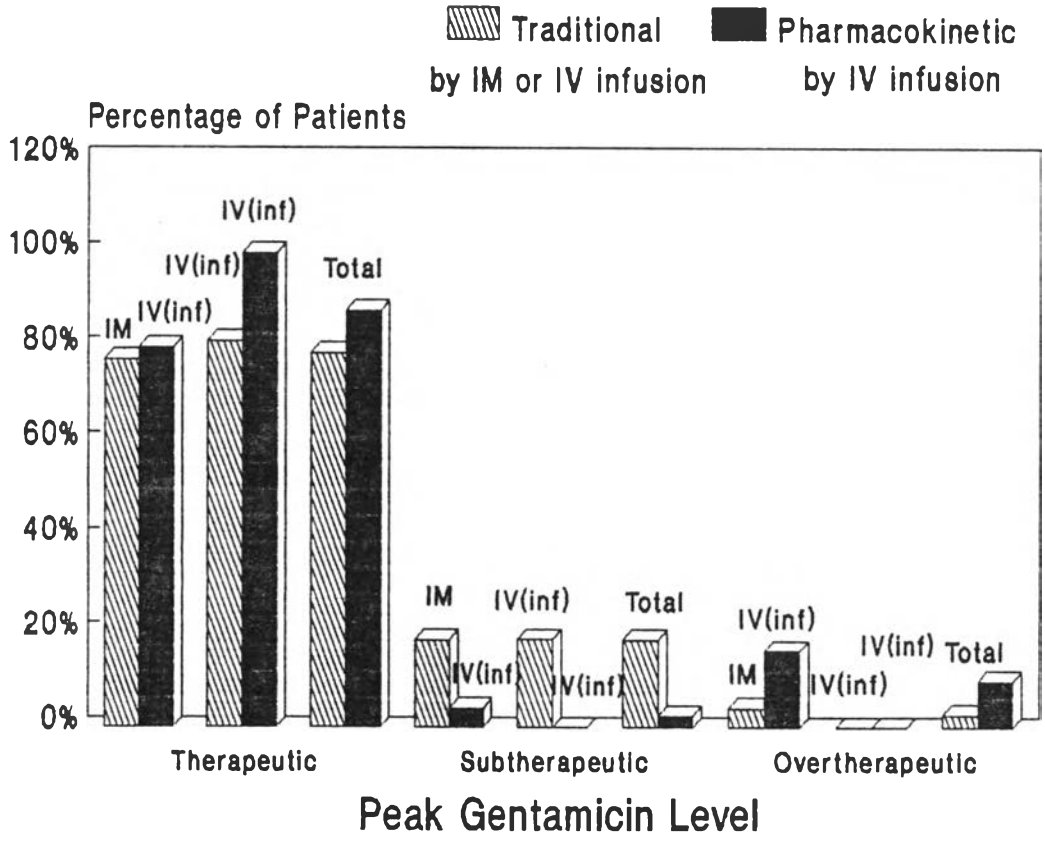
Peak concentration within	Percentage of Patients (N)					
	Initial dosage regimen (Traditional method)			After dosage adjustment (Pharmacokinetic method)		
	IM	IV(inf)	Total	IV(inf)	IV(inf)	Total
T	77.55(38)	81.48(22)	78.95(60)	80(20)	100(16)	87.80(36)
S	18.37(9)	18.52(5)	18.42(14)	4(1)	-	2.44(1)
O	4.08(2)	-	2.63(2)	16(4)	-	9.76(4)

Figure 1 Comparison between Traditional and Pharmacokinetic method

A : Both Peak and Trough were considered



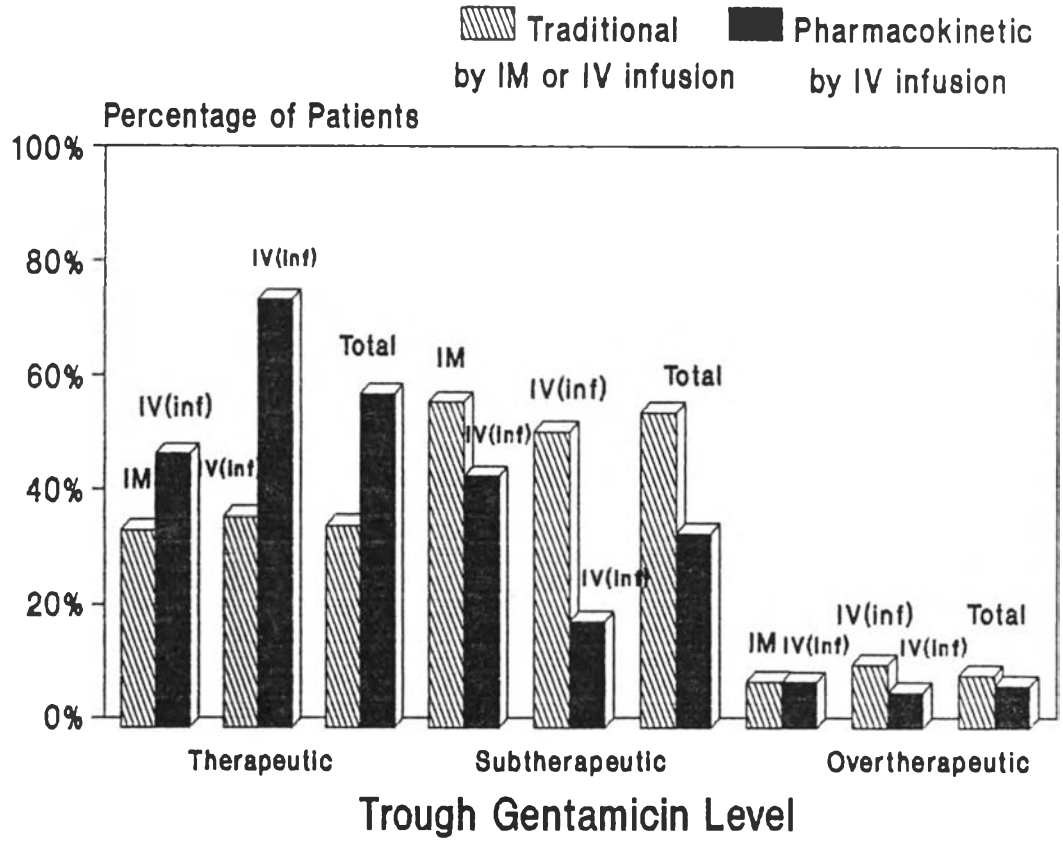
B : Peak concentration only was considered



C : Trough only was considered.

Trough concentration within	Percentage of Patients (N)					
	Initial dosage regimen (Traditional method)			After dosage adjustment (Pharmacokinetic method)		
	IM	IV(inf)	Total	IV(inf)	IV(inf)	Total
T	34.69(17)	37.04(10)	35.53(27)	48(12)	75(12)	58.54(24)
S	57.14(28)	51.85(14)	55.26(42)	44(11)	18.75(3)	34.15(14)
O	8.16(4)	11.11(3)	9.21(7)	8(2)	6.25(1)	7.32(3)

C : Trough concentration only was considered



obtained when peak only was considered while table 6C and figure 1C showed the result obtained when trough only was considered.

The result showed that the percentage of patients whose peak and/or trough serum gentamicin concentrations were within the therapeutic range was obviously higher after the drug was administered with pharmacokinetic calculated dosage regimen as compared with those obtained after the drug was administered with traditional dosage regimen. The percentage of improvement was much higher if the drug was initially given by IV infusion method as compare to those patients who received the drug initially by IM method. There were lower percentage of patients whose peak and/or trough concentrations was within the subtherapeutic range after the drug was given with the pharmacokinetic calculated dosage regimen. However, the percentage of patients whose peak concentration was in the overtherapeutic range was a litle bit higher after dosage adjustment in the group of patients who initially received the drug by IM method.

III Comparison Among Different Methods used for Serum Gentamicin Concentration Prediction

1. Comparison between the equation generated from foreign population and the equation generated from Thai population

One of the method generally used for predicting gentamicin concentrations was to estimate the elimination

rate constant (Kel) from patients' serum creatinine concentration using equation previously generated from the population's parameters. The equation extensively used in the hospital in the United States has been published in several literatures.

One of the purpose here was to compare the equation generated from foreign population to the equation generated from Thai population. Table 7 showed the creatinine clearance (CrCl) (obtained from knowing the patient's serum creatinine) and the elimination rate constant (Kel) (obtained from knowing the patient's serum gentamicin concentrations) of twenty Thai patients. Figure 2 showed the linear regression of Kel versus CrCl from table 7 and the linear equation obtained was identified as the equation generated from Thai population. Table 8 compared the elimination rate constant of twenty Thai population patients (not the same group as above), obtained from equations generated from foreign population and from Thai population, the volume of distribution of each individual included in the table was calculated from the mean value 0.26 L/kg. Table 9 showed comparison between measured serum gentamicin concentration and the predicted gentamicin concentrations while table 10A showed the bias and precision of the predicted methods and table 10B showed statistical test comparing the two predicted methods.

The result obtained showed that the equation generated from Thai population will give less bias and better precision when used to predict the peak and

Table 7 Elimination rate constant (Kel) and Creatinine clearance (CrCl) of the first 20 patients.

Patient Number	CrCl[1] (ml/min)	Kel(blood)[2] ($hour^{-1}$)
1	110.9247	0.2430
2	37.9818	0.1179
3	85.5924	0.1424
4	25.5570	0.1031
5	99.6484	0.3416
6	57.9208	0.2271
7	98.1482	0.2947
8	108.3271	0.2286
9	92.4768	0.2612
10	89.1204	0.3146
11	113.9227	0.3343
12	92.4211	0.4183
13	70.0798	0.1966
14	106.6503	0.3234
15	47.9601	0.2508
16	84.7953	0.2287
17	84.8131	0.2971
18	43.7744	0.0530
19	52.0610	0.1628
20	86.8471	0.2219

[1] Creatinine clearance was calculated from equation 1-4 (Appendix A)

[2] Elimination rate constant was calculated from serum gentamicin concentration using equation 7 (Appendix A)

Figure 2 Graph plot between Kel(blood) and CrCl

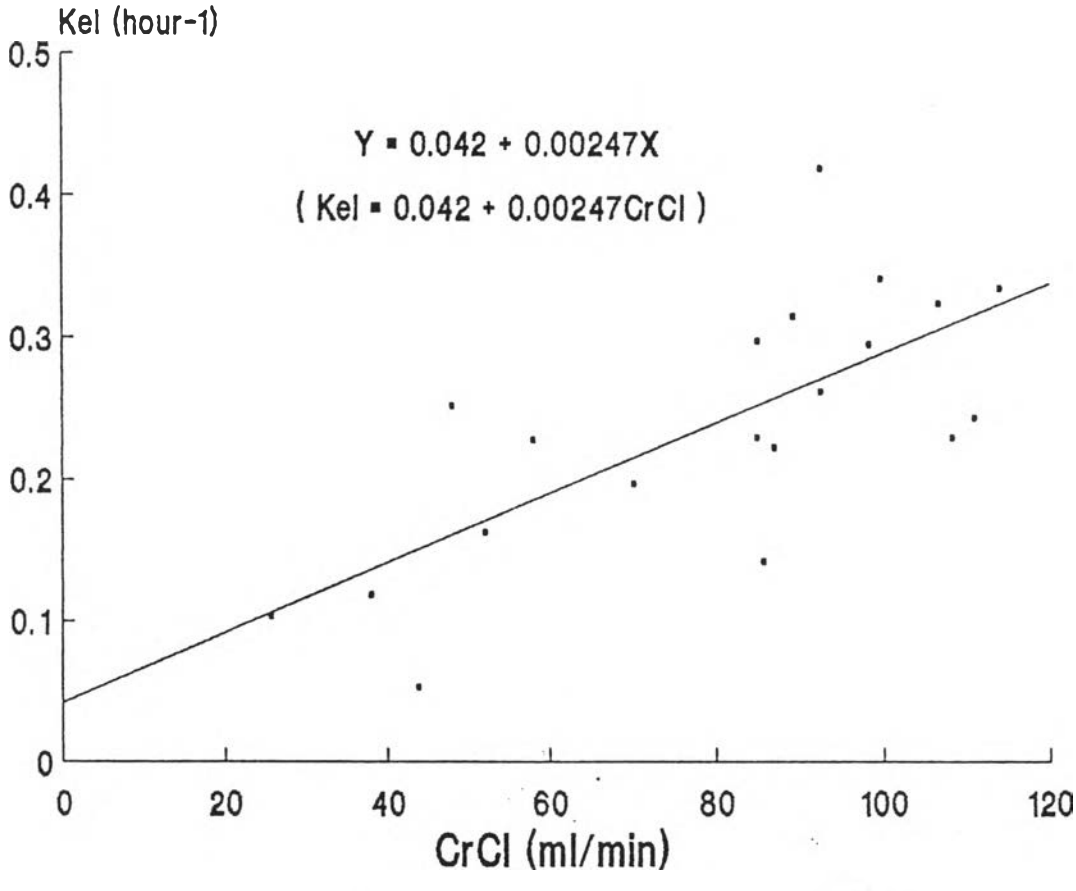


Table 8 Comparison of the Elimination Rate Constant and Volume of Distribution estimated from serum creatinine using the Equations Generated from Foreign population and from Thai population

Patient Number	$Kel(scr)_F$[1] ($hour^{-1}$)	$Kel(Scr)_T$[2] ($hour^{-1}$)	Vd(mean)[3] (L)
21	0.1474	0.1795	10.92
25	0.2070	0.2413	11.70
26	0.2460	0.2817	14.30
29	0.2289	0.2640	13.00
36	0.1214	0.1524	11.44
37	0.3022	0.3400	12.22
38	0.3434	0.3828	12.22
39	0.2490	0.2848	16.90
40	0.1163	0.1471	12.48
44	0.2277	0.2627	20.28
52	0.1660	0.1987	11.70
53	0.2758	0.3126	20.80
55	0.3627	0.4028	11.70
60	0.1826	0.2160	22.10
63	0.1909	0.2246	11.18
69	0.2644	0.3008	18.20
70	0.2110	0.2454	15.60
72	0.2706	0.3073	16.90
75	0.2001	0.2341	14.56
82	0.3885	0.4296	15.60

[1] $Kel(Scr)_F$ = Elimination rate constant calculated from foreign population parameter ($Kel(Scr)_F = 0.015 + 0.00238 \times CrCl$)

[2] $Kel(Scr)_T$ = Elimination rate constant calculated from Thai population parameter ($Kel(Scr)_T = 0.042 + 0.00247 \times CrCl$)

[3] Vd (mean) = Mean population volume of distribution (Vd = 0.26 L/kg)

Table 9 Comparison between the Predicted serum gentamicin concentration using individual pharmacokinetic value from Table 8 and the Measured serum gentamicin concentration

Patient Number	Measured Trough (µg/ml)	Predicted by method		Measured Peak (µg/ml)	Predicted by method	
		I (µg/ml)	II (µg/ml)		I (µg/ml)	II (µg/ml)
21	1.03	2.53	1.80	4.85	7.65	6.90
25	0.45	1.70	1.23	4.89	8.03	7.54
26	0.60	0.97	0.70	5.08	6.12	5.83
29	0.45	0.93	0.68	3.04	5.19	4.92
36	2.21	4.39	3.05	7.59	10.92	9.56
37	2.23	0.69	0.50	4.83	6.67	6.44
38	0.67	0.37	0.27	3.58	4.82	4.69
39	0.55	0.80	0.58	5.58	5.15	4.92
40	1.74	4.30	2.96	6.80	10.28	8.93
44	0.55	0.81	0.59	4.33	4.45	4.21
52	0.84	2.57	1.84	5.67	8.93	8.18
53	0.49	0.64	0.46	4.48	5.05	4.85
55	1.53	0.44	0.31	4.82	6.62	6.45
60	1.79	1.14	0.83	4.46	4.50	4.17
63	1.94	2.08	1.51	7.30	8.72	8.11
69	0.60	0.64	0.47	3.81	4.69	4.48
70	0.67	1.23	0.89	3.59	5.97	5.61
72	1.39	0.66	0.48	4.55	5.00	4.80
75	0.73	1.46	1.06	4.97	6.55	6.13
82	1.09	0.20	0.14	3.59	3.66	3.58

Method I = Pedicted gentamicin concentration estimated by $Kel(Scr)_F$, Vd (mean)

Method II = Predicted gentamicin concentration estimated by $Kel(Scr)_T$, Vd (mean)

Table 10A Measurement of absolute performance for predicted peak and trough*

Method	Bias		Precision	
	Mean prediction error(me)		Mean squared prediction error(mse)	
	Trough	Peak	Trough	Peak
I	0.35±0.24	1.56±0.27	1.24±0.40	3.85±0.94
II	-0.06±0.18	1.12±0.22	0.60±0.17	2.19±0.50

*All data are expressed as mean±SD in μg/ml

Method I : predicted by $Kel(Scr)_F$, Vd (mean)

Method II : predicted by $Kel(Scr)_T$, Vd (mean)

Table 10B Measurement of relative performance for predicted peak and trough

Method	Trough				Peak			
	Bias Δme (CFDI)	statistic test	Precision Δmse (CFDI)	Statistic test	Bias Δme (CFDI)	statistic test	Precision Δmse (CFDI)	statistic test
I VS II	0.41 (0.24,0.58)	S	0.64 (-0.07,1.35)	NS	0.44 (0.27,0.61)	S	1.66 (0.57,2.75)	S

(CFDI) = 95% confidence interval

S = Significant (confidence interval did not include zero)

NS = No Significant (confidence interval included zero)

trough serum gentamicin as compared to the equation generated from foreign population.

2. Comparison among four different pairs of pharmacokinetic parameters were used to predict serum gentamicin concentrations

Majority of the equations used to predict serum gentamicin concentrations required the estimation of the individual patient's two significant parameters, i.e., the elimination rate constant and the volume of distribution.

The elimination rate constant of the patient could be obtained from several methods. It could either be calculated from the equation generated from foreign population or from the equation generated from Thai population as a forementioned which was based on the patient's physical characteristics, such as,weight,height, age, etc and the serum creatinine concentration. These methods did not require any data about serum gentamicin concentrations. However, if at least two serum gentamicin concentrations were known, the elimination rate constant could be calculated directly from these two known concentrations.

The volume of distribution, on the other hand,were usually obtained by using the population's mean value, i.e., the volume of distribution of gentamicin is 0.26 L/kg. If at least two serum gentamicin concentrations were known, the volume of distribution of each individual patient could be obtained from equation 9 and was called Vd(blood)(Appendix A)

Table 11 showed the elimination rate constants obtained from three different methods, i.e., equation obtained from foreign population, equation obtained from Thai population and obtained directly from two known serum gentamicin concentration. Also included in table 11 were the volume of distribution calculated from the population's mean vulue and calculated from the known serum drug concentrations.

Table 12 showed the measured peak and trough concentration of each patient along with the predicted values from four methods. The first method used the elimination rate constant obtained from foreign generated equation, $Kel(Scr)_F$, and the volume of distribution which was calculated from the population's mean value, Vd(mean). The second method used the elimination rate constant obtained from Thai population, $Kel(Scr)_T$, and the volume of distribution which was calculated from the population's mean value, Vd(mean). The third method used the elimination rate constant obtained directly from two known serum gentamicin concentration, Kel(blood), and the volume of distribution which was calculated from the population's mean value, Vd(mean). The forth method used the elimination rate constant obtained directly from two known serum gentamicin concentration, Kel(blood), and the volume of distribution which was calculated from the population's mean value, Vd(mean), and/or from serum gentamicin concentration.

Table 13a and 13b showed the comparison among four different methods by measurement of the bias and the

precision of each predicted method as compared to the measured value and also the statistical test for the significant difference between methods.

The result showed that the fourth method which used the elimination rate constant estimated from serum gentamicin concentration and the volume of distribution estimated from serum gentamicin concentration where possible (If the drug was administered initially by IV infusion, the volume of distribution could be estimated from serum gentamicin concentration. On the other hand, if the drug was administered initially by IM, the volume of distribution could not be estimated from serum gentamicin concentration. The population's mean value would be used in these cases) showed least bias and best precision as compared to the measured value. Statistical test between methods showed that the third method resulted in significant higher bias but not significant in precision than the forth method. The second and the third methods were not significantly different from each other in both bias and precision. The first method, on the other hand, was significantly different from the second, the third and the fourth methods in both the bias and the precision of most values.

It was therefore came to the conclusion that whenever possible the serum gentamicin concentrations of the patients should be obtained and the elimination rate constant and volume of distribution should be estimated from these serum concentrations. This would be the most accurate parameters used for predicting the later

Table 11 Comparison of the Elimination rate constant and volume of distribution estimated from serum creatinine and serum gentamicin concentration in patients whose dosage regimen were adjusted by pharmacokinetic method.

Patient Number	Kel(Scr)$_F$[1]	Kel(Scr)$_T$[2]	Kel(blood)[3]	Vd(mean)[4]	Vd(blood)[5]
4	0.0758	0.1051	0.1031	11.18	13.32
5	0.2522	0.2881	0.3416	13.52	17.79
8	0.2728	0.3096	0.2286	17.16	-
9	0.2351	0.2704	0.2612	12.22	-
11	0.2861	0.3234	0.3343	15.34	-
12	0.2350	0.2703	0.4183	12.74	-
14	0.2689	0.3054	0.3234	15.86	-
16	0.2168	0.2514	0.2287	15.08	26.19
17	0.2169	0.2515	0.2971	14.04	20.03
18	0.1192	0.1501	0.0530	16.64	-
19	0.1389	0.1706	0.1628	12.22	-
20	0.2217	0.2565	0.2219	16.12	-
22	0.2832	0.3203	0.2637	16.12	-
25	0.2070	0.2413	0.3408	11.70	16.31
26	0.2460	0.2817	0.3052	14.30	16.25
29	0.2289	0.2640	0.2729	13.00	21.19
32	0.2500	0.2859	0.2259	14.82	-
35	0.3039	0.3418	0.2708	15.08	-
36	0.1214	0.1524	0.1763	11.44	13.76
37	0.3022	0.3400	0.1104	12.22	28.62
38	0.3434	0.3828	0.2394	12.22	18.94

Continued .....

Patient Number	Kel(Scr)$_F$[1]	Kel(Scr)$_T$[2]	Kel(blood)[3]	Vd(mean)[4]	Vd(blood)[5]
39	0.2490	0.2848	0.3310	16.90	14.42
41	0.2012	0.2352	0.3055	11.96	-
42	0.2262	0.2612	0.3349	14.82	-
50	0.2633	0.2997	0.3421	14.30	-
51	0.2305	0.2656	0.4455	16.38	-
52	0.1660	0.1987	0.2728	11.70	15.15
58	0.1471	0.1791	0.3015	11.96	-
59	0.2404	0.2759	0.1208	14.04	-
61	0.2084	0.2427	0.2458	11.18	-
64	0.2936	0.3311	0.3337	16.90	-
68	0.2106	0.2450	0.2829	12.48	-
69	0.2644	0.3008	0.2641	18.20	22.82
70	0.2110	0.2454	0.2238	15.60	25.30
71	0.1710	0.1001	0.1334	15.60	-
75	0.2001	0.2341	0.2740	14.56	17.25
77	0.2117	0.2461	0.3254	10.92	-
78	0.3553	0.3952	0.3015	14.30	-
80	0.0932	0.1232	0.0674	20.02	-
82	0.3885	0.4296	0.1703	15.60	22.22

[1] Kel(Scr)$_F$ = Elimination rate constant calculated from foreign population parameter

[2] Kel(Scr)$_T$ = Elimination rate constant calculated from Thai population parameter

[3] Kel(blood) = Elimination rate constant calculated from serum concentration

[4] Vd(mean) = Volume of distribution calculated from mean Vd(=0.26 L/kg)

[5] Vd(blood) = Volume of distribution calculated from serum concentration

Table 12 Comparison between the Predicted serum gentamicin concentration estimated by using individual pharmacokinetic value from Table 11 and the Measured serum gentamicin concentration

Patient Number	Measured Trough	Predicted by method				Meaured Peak	Predicted by method			
		I	II	III	IV		I	II	III	IV
	(μg/ml)	(μg/ml)	(μg/ml)	(μg/ml)	(μg/ml)	(μg/ml)	(μg/ml)	(μg/ml)	(μg/ml)	(μg/ml)
4	3.59	3.69	2.18	2.25	1.89	6.02	8.81	7.29	7.37	6.18
5	1.13	2.23	1.72	1.19	0.91	8.65	8.91	8.37	7.80	5.93
8	0.35	0.71	0.52	1.06	1.06	5.20	5.53	5.30	5.90	5.90
9	1.36	1.33	0.97	1.05	1.05	7.35	7.74	7.35	7.44	7.44
11	1.18	1.38	1.07	0.99	0.99	6.57	6.66	6.33	6.24	6.24
12	2.35	2.42	1.86	0.70	0.70	7.77	8.82	8.23	6.94	6.94
14	0.90	1.51	1.17	1.03	1.03	6.05	6.63	6.26	6.12	6.12
16	1.32	1.50	1.09	1.34	0.77	8.16	7.63	7.19	7.46	4.30
17	0.48	2.67	2.05	1.48	1.03	5.37	8.81	8.16	7.56	5.30
18	0.70	0.30	0.14	1.90	1.90	5.44	4.95	4.76	6.59	6.59
19	0.47	1.38	0.89	0.99	0.99	3.39	6.82	6.30	6.41	6.41
20	0.63	1.07	0.78	1.07	1.07	4.78	5.66	5.34	5.66	5.66
22	0.48	0.69	0.51	0.82	0.82	3.34	5.81	5.59	5.95	5.59
25	0.73	3.29	2.51	1.25	0.89	5.19	10.28	9.47	8.12	5.83
26	1.16	1.76	1.36	1.15	1.01	6.36	6.82	6.40	6.18	5.44
29	0.82	2.76	2.12	1.99	1.22	8.02	9.73	9.07	8.93	5.48
32	0.74	0.90	0.66	1.12	1.12	5.05	5.87	5.60	6.11	6.11
35	0.75	1.10	0.85	1.39	1.39	4.94	5.87	5.60	6.18	6.18
36	1.84	3.29	2.28	1.77	1.47	7.73	8.19	7.17	6.64	5.52
37	1.29	0.24	0.15	3.05	1.30	3.54	7.80	7.66	10.84	4.63
38	1.91	1.30	1.01	2.71	1.75	7.53	8.62	8.28	10.12	6.53
39	2.33	1.82	1.41	1.02	1.20	7.91	7.18	6.74	6.32	7.41

Continued .....

Patient Number	Measured Trough (µg/ml)	Predicted by method I (µg/ml)	II (µg/ml)	III (µg/ml)	IV (µg/ml)	Measured Peak (µg/ml)	Predicted by method I (µg/ml)	II (µg/ml)	III (µg/ml)	IV (µg/ml)
41	0.37	3.00	2.29	1.38	1.38	3.95	9.08	8.34	7.38	7.38
42	0.11	2.48	1.90	1.14	1.14	16.63	8.59	7.99	7.18	7.18
50	0.79	1.94	1.50	1.12	1.12	5.21	8.25	7.78	7.38	7.38
51	1.00	2.17	1.66	0.51	0.51	6.21	7.70	7.17	5.88	5.88
52	1.24	3.21	2.30	1.16	0.90	6.12	11.16	10.22	9.00	6.96
58	0.30	3.09	2.19	0.71	0.71	5.13	9.32	8.40	6.82	6.82
59	0.60	0.36	0.23	1.80	1.80	9.81	5.69	5.52	7.22	7.22
61	1.02	1.75	1.27	1.24	1.24	4.07	8.38	7.87	7.83	7.83
64	1.02	1.32	1.02	1.00	1.00	6.46	6.64	6.32	6.30	6.30
68	0.67	2.66	2.04	1.54	1.54	6.26	8.48	7.83	7.32	7.32
69	1.47	1.51	1.17	1.52	1.21	4.16	6.47	6.11	6.47	5.16
70	2.31	2.65	2.03	2.40	1.48	6.02	8.47	7.83	8.21	5.06
71	1.74	3.88	2.26	1.34	1.34	5.67	8.78	7.15	6.21	6.21
75	1.08	2.49	1.90	1.41	1.19	5.74	7.49	6.87	6.36	5.37
77	1.29	3.02	2.31	1.32	1.32	10.63	9.67	8.93	7.88	7.88
78	1.15	0.82	0.64	1.18	1.18	5.15	5.82	5.60	6.21	6.21
80	1.89	0.49	0.23	1.01	1.01	5.52	4.37	4.09	4.90	4.90
82	0.65	0.33	0.24	2.30	1.62	6.03	6.10	5.96	8.26	5.80

Method I = Predicted gentamicin concentration estimated by using Kel(Scr)F,Vd(mean)

Method II = Predicted gentamicin concentration estimated by using Kel(Scr)T,Vd(mean)

Method III = Predicted gentamicin concentration estimated by using Kel(blood), Vd(mean)

Method IV = Predicted gentamicin concentration estimated by using Kel(blood), Vd(blood) and Vd (mean)

Table 13A Measurement of absolute performance for predicted peak and trough*

Method	Bias		Precision	
	Mean prediction error(me)		Mean squared prediction error(mse)	
	Trough	Peak	Trough	Peak
I	0.71±0.16	1.26±0.39	1.56±0.21	7.60±1.93
II	0.21±0.14	0.73±0.38	0.78±0.17	6.11±2.00
III	0.23±0.12	0.76±0.40	0.58±0.13	6.68±2.53
IV	0.03±0.11	-0.10±0.36	0.44±0.11	5.06±2.25

*All data are expressed as mean±SD in µg/ml

Method I = Predicted gentamicin concentration estimated by using Kel(Scr)F,Vd(mean)

Method II = Predicted gentamicin concentration estimated by using Kel(Scr)T,Vd(mean)

Method III = Predicted gentamicin concentration estimated by using Kel(blood), Vd(mean)

Method IV = Predicted gentamicin concentration estimated by using Kel(blood), Vd(blood) and Vd (mean)

Table 13B Measurement of relative performance for predicted peak and trough

Method	Trough				Peak			
	Bias Δme (CFDI)	statistic test	precision Δmse (CFDI)	statistic test	Bias Δme (CFDI)	statistic test	precision Δmse (CFDI)	statistic test
I VS II	0.50 (0.40,0.60)	S	0.78 (0.34,1.22)	S	0.53 (0.43,0.63)	S	1.49 (0.44,2.54)	S
I VS III	0.48 (0.10,0.86)	S	0.98 (0.23,1.73)	S	0.50 (0.10,0.90)	S	0.92 (-2.03,3.8)	NS
I VS IV	0.68 (0.34,1.02)	S	1.12 (0.37,1.87)	S	1.36 (0.85,1.86)	S	2.54 (-0.35,5.43)	NS
II VS III	0.02 (-0.28,0.32)	NS	0.20 (-0.20,0.60)	NS	0.03 (-0.29,0.35)	NS	0.57 (-1.75,2.89)	NS
II VS IV	0.18 (-0.08,0.44)	NS	0.34 (-0.04,0.72)	NS	0.83 (0.38,1.27)	s	2.54 (-0.35,5.43)	NS
III VS IV	0.20 (0.08,0.32)	S	0.14 (-0.06,0.34)	NS	0.86 (0.40,1.32)	S	1.62 (-1.25,4.49)	NS

CFDI = 95% confidence interval

S = Significant (confidence interval did not include zero)

NS = No significant (confidence interval included zero)

serum drug concentrations. If the volume of distribution could not be obtained from serum concentrations as in the case which the drug was initially given by IM method and the population's mean value for volume of distribution should be used, the use of pre-generated equation from Thai population (the second method) or the use of individual serum drug concentrations (the third method) to estimate the elimination rate constant would result in the same accuracy in prediction. The elimination rate constant obtained from equation pre-generated from foreign population would give highest bias and least precision when applied to predict the later serum drug concentrations or calculated the suitable dosage regimen.

Effect of the initially route of administration, IV infusion or IM was also analyzed separately. Table 14, table 15A and table 15A showed the result of patients who initially received gentamicin by IV infusion only while table 16, table 17A and table 17B included only the result of patients who initially received gentamicin by IM. The result obtained indicated that if dosage adjustment was required in patient who initially received gentamicin by IV infusion and the serum drug concentrations of the patients could be obtained, these data should be used to estimate both the elimination rate constant and volume of distribution of the individual patient (the forth method), then the least bias and precision error could be obtained. However, if the patient's serum drug concentration could not be obtained, the pre-generated equation from Thai population (the second method) should be used to estimate the elimination

Table 14 Comparison between the Predicted serum gentamicin concentration estimated by using individual pharmacokinetic value from Table 11 and the Measured serum gentamicin concentration

(Patients initially received gentamicin by IV infusion only were included)

Patient Number	Measured Trough (µg/ml)	Predicted by method				Measured Peak (µg/ml)	Predicted by method			
		I (µg/ml)	II (µg/ml)	III (µg/ml)	IV (µg/ml)		I (µg/ml)	II (µg/ml)	III (µg/ml)	IV (µg/ml)
4	3.59	3.69	2.18	2.25	1.89	6.02	8.81	7.29	7.37	6.18
5	1.13	2.23	1.72	1.19	0.91	8.65	8.91	8.37	7.80	5.93
16	1.32	1.50	1.09	1.34	0.77	8.16	7.63	7.19	7.46	4.30
17	0.48	2.67	2.05	1.48	1.03	5.37	8.81	8.16	7.56	5.30
25	0.73	3.29	2.51	1.25	0.89	5.19	10.28	9.47	8.12	5.83
26	1.16	1.76	1.36	1.15	1.01	6.36	6.82	6.40	6.18	5.44
29	0.82	2.76	2.12	1.99	1.22	8.02	9.73	9.07	8.93	5.48
36	1.84	3.29	2.28	1.77	1.47	7.73	8.19	7.17	6.64	5.52
37	1.29	0.24	0.15	3.05	1.30	3.54	7.80	7.66	10.84	4.63
38	1.91	1.30	1.01	2.71	1.75	7.53	8.62	8.28	10.12	6.53
39	2.33	1.82	1.41	1.02	1.20	7.91	7.18	6.74	6.32	7.41
52	1.24	3.21	2.30	1.16	0.90	6.12	11.16	10.22	9.00	6.96
69	1.47	1.51	1.17	1.52	1.21	4.16	6.47	6.11	6.74	5.16
70	2.31	2.65	2.03	2.40	1.48	6.02	8.47	7.83	8.21	5.06
75	1.08	2.49	1.90	1.41	1.19	5.74	7.49	6.87	6.36	5.37
82	0.65	0.33	0.24	2.30	1.62	6.30	6.10	5.96	8.26	5.80

Method I = Predicted gentamicin concentration estimated by Kel(Scr)F,Vd(mean)

Method II = Predicted gentamicin concentration estimated by Kel(Scr)T,Vd(mean)

Method III = Predicted gentamicin concentration estimated by Kel(blood),Vd(mean)

Method IV = Predicted gentamicin concentration estimated by Kel(blood),Vd(blood)'

Table 15A Measurement of absolute performance for predicted peak and trough*

Method	Bias		Precision	
	Mean prediction error(me)		Mean squared prediction error(mse)	
	Trough	Peak	Trough	Peak
I	0.71±0.28	1.87±0.47	1.67±0.30	6.81±2.22
II	0.14±0.25	1.26±0.45	0.94±0.24	4.64±1.65
III	0.23±0.23	1.25±0.56	0.84±0.26	6.31±3.22
IV	-0.22±0.16	-0.73±0.36	0.44±0.19	2.51±1.02

*All data are expressed as mean±SD in μg/ml

Method I = Predicted gentamicin concentration estimated by Kel(Scr)F,Vd(mean)

Method II = Predicted gentamicin concentration estimated by Kel(Scr)T,Vd(mean)

Method III = Predicted gentamicin concentration estimated by Kel(blood),Vd(mean)

Method IV = Predicted gentamicin concentration estimated by Kel(blood),Vd(blood)

Table 15B Measurement of relative performance for predicted peak and trough

Method	Trough				Peak			
	Bias Δme (CFDI)	statistic test	Precision Δmse (CFDI)	statistic test	Bias Δme (CFDI)	statistic test	precision Δmse (CFDI)	statistic test
I VS II	0.57 (0.38,0.76)	S	0.74 (-0.03,1.51)	NS	0.61 (0.42,0.80)	S	2.17 (0.61,3.73)	S
I VS III	0.48 (-0.27,1.23)	NS	0.83 (-0.47,2.13)	NS	0.62 (-0.17,1.41)	NS	0.5 (-5.64,6.64)	NS
I VS IV	0.93 (0.33,1.53)	S	1.23 (-0.05,2.51)	NS	2.6 (1.88,3.32)	S	4.3 (-1.54,10.14)	NS
II VS III	0.09 (-0.53,0.71)	NS	0.1 (-0.56,0.76)	NS	0.01 (-0.67,0.69)	NS	1.67 (-3.68,7.02)	NS
II VS IV	0.36 (-0.09,0.81)	NS	0.5 -0.10,1.10)	NS	1.99 (1.31,2.67)	S	2.13 (-2.52,6.78)	NS
III VS IV	0.45 (0.22,0.68)	S	0.65 (0.10,1.22)	S	1.98 (1.11,2.85)	S	3.80 (-3.74,11.34)	NS

CFDI = confidence interval

S = Significant (confidence interval did not include zero)

NS = No significant (confidence interval included zero)

Table 16 Comparison between the Predicted serum gentamicin concentration estimated by using individual pharmacokinetic value from Table 11 and the Measured serum gentamicin concentration

(Patients initially received gentamicin by IM only were included)

Patient Number	Measured Trough	Predicted by method I (μg/ml)	Predicted by method II (μg/ml)	Predicted by method III (μg/ml)	Measured Peak	Predicted by method I (μg/ml)	Predicted by method II (μg/ml)	Predicted by method III (μg/ml)
8	0.35	0.71	0.52	1.06	5.20	5.53	5.30	5.90
9	1.36	1.33	0.97	1.05	7.35	7.74	7.35	7.44
11	1.18	1.38	1.07	0.99	6.57	6.66	6.33	6.24
12	2.35	2.42	1.86	0.70	7.77	8.82	8.23	6.94
14	0.90	1.51	1.17	1.03	6.05	6.63	6.26	6.12
18	0.70	0.30	0.14	1.90	5.44	4.95	4.76	6.59
19	0.47	1.38	0.89	0.99	3.39	6.82	6.30	6.41
20	0.63	1.07	0.78	1.07	4.78	5.66	5.34	5.66
22	0.48	0.69	0.51	0.82	3.34	5.81	5.59	5.95
32	0.74	0.90	0.66	1.12	5.05	5.87	5.60	6.11
35	0.75	1.10	0.85	1.39	4.94	5.87	5.60	6.18
41	0.37	3.00	2.29	1.38	3.95	9.08	8.34	7.38
42	0.11	2.48	1.90	1.14	16.63	8.59	7.99	7.18
50	0.79	1.94	1.50	1.12	5.21	8.25	7.78	7.38
51	1.00	2.17	1.66	0.51	6.21	7.70	7.17	5.88
58	0.30	3.09	2.19	0.71	5.13	9.32	8.40	6.82
59	0.60	0.36	0.23	1.80	9.81	5.69	5.52	7.22
61	1.02	1.75	1.27	1.24	4.07	8.38	7.87	7.83
64	1.02	1.32	1.02	1.00	6.46	6.64	6.32	6.30
68	0.67	2.66	2.04	1.54	6.26	8.48	7.83	7.32

Continued .....

Patient Number	Measured Trough	Predicted by method I (µg/ml)	Predicted by method II (µg/ml)	Predicted by method III (µg/ml)	Measured Peak	Predicted by method I (µg/ml)	Predicted by method II (µg/ml)	Predicted by method III (µg/ml)
71	1.74	3.88	2.26	1.34	5.67	8.78	7.15	6.21
77	1.29	3.02	2.31	1.32	10.63	9.67	8.93	7.88
78	1.15	0.82	0.64	1.18	5.15	5.82	5.60	6.21
80	1.89	0.49	0.23	1.01	5.52	4.34	4.09	4.90

Method I = Predicted gentamicin concentration estimated by Kel(Scr)P,Vd(mean)

Method II = Predicted gentamicin concentration estimated by Kel(Scr)T,Vd(mean)

Method III = Predicted gentamicin concentration estimated by Kel(blood),Vd(mean)

Table 17A Measurement of absolute performance for perdicted peak and trough*

Method	Bias		Precision	
	Mean prediction error (me)		Mean squared prediction error (mse)	
	Trough	Peak	Trough	Peak
I	0.71±0.21	0.86±0.57	1.48±0.29	8.12±2.89
II	0.25±0.16	0.38±0.55	0.68±0.23	7.09±3.17
III	0.19±0.13	0.31±0.54	0.45±0.13	6.76±3.69

*All data are expressed as mean±SD in μg/ml

Method I = Predicted gentamicin concentration estimated by Kel(Scr)F,Vd(mean)

Method II = Predicted gentamicin concentration estimated by Kel(Scr)T,Vd(mean)

Method III = Predicted gentamicin concentration estimated by Kel(blood),Vd(mean)

Table 17B Measurement of relative performance for predicted peak and trough

Method	Trough				Peak			
	Bias Δme (CFDI)	statistic test	Precision Δmse (CFDI)	statistic test	Bias Δme (CFDI)	statistic test	Precision Δmse (CFDI)	statistic test
I VS II	0.46 (0.32,0.60)	S	0.8 (0.22,1.38)	S	0.48 (0.36,0.60)	S	1.03 (-0.40,2.50)	NS
I VS III	0.52 (0.06,0.98)	S	1.03 (0.04,2.02)	S	0.55 (0.07,1.03)	S	1.36 (-1.83,4.55)	NS
II VS III	0.06 (-0.29,0.41)	NS	0.23 (-0.29,0.75)	NS	0.07 (-0.30,0.44)	NS	0.33 (-1.66,2.32)	NS

CFDI = confidence interval

S = Significant (confidence interval did not include zero)

NS = No significant (confidence interval included zero)

rate constant. The elimination rate constant estimated from equation generated from foreign population (the first method)would give the least accurate result. For patients who initially received gentamicin by IM route, only three methods were compared since the forth method required the estimation of the volume of distribution from serum drug concentration which could not be obtained from IM route. The elimination rate constant either estimated from serum drug concentrations (the third method) or estimated from equation pre-generated from Thai population did not show any significant difference when applied to predict the later serum drug concentrations. However, the elimination rate constant estimated from equation pre-generated from foreign population (the first method) showed least accuracy result and was significantly different from the second and the third method.

Comparison among different methods used to estimate the pharmacokinetic parameters for those patients who initially received gentamicin by IV push was also performed. The elimination rate constant estimated from individual patient's serum drug concentration (the third method) gave the most accurate result, while the elimination rate constant estimated from equation generated from Thai population (the second method) was rank the second and the elimination rate constant estimated from equation generated from foreign population (the first method) was the least accurate. However , the number of patient included in this group (N) was only three, higher number of the patients in this group should be obsereved in order to back up these results.

Table 18 Comparison of the Elimination rate constant and Volume of distribution estimated from serum creatinine and serum gentamicin concentration in patients who were initially received IV push by traditional method.

Patient Number	$kel(scr)_F$	$kel(scr)_T$	kel(blood)	Vd(mean)
48	0.2035	0.2377	0.3102	10.14
56	0.1530	0.1852	0.2930	8.84
73	0.1248	0.1560	0.2118	14.30

Table 19 Comparison between the Predicted serum gentamicin concentration estimated using individual pharmacokinetic value from table 18 and the Measured serum gentamicin concentration (Patients initially received gentamicin by IV push only)

Patients	Messured	Predicted by method			Measured	Predicted by method		
Number	Trough (µg/ml)	I (µg/ml)	II (µg/ml)	III (µg/ml)	Peak (µg/ml)	I (µg/ml)	II (µg/ml)	III (µg/ml)
48	1.54	2.03	1.47	0.78	7.79	9.33	8.74	7.98
56	0.79	3.92	2.79	1.03	7.64	12.34	11.18	9.31
73	1.54	3.37	2.34	1.33	5.32	8.59	7.55	6.50

Table 20A Measurement of absolute performance for predicted peak and trough*

Method	Bias		Precision	
	Mean prediction error(me)		Mean squared prediction error (mse)	
	Trough	Peak	Trough	Peak
I	1.81±0.76	3.17±0.91	4.45±2.81	11.72±5.72
II	0.91±0.60	2.24±0.75	1.55±1.24	6.15±3.42
III	-0.24±0.29	1.01±0.44	0.23±0.18	1.41±0.80

*All data are expressed as mean±SD in µg/ml

Method I = Predicted gentamicin concentration estimated by Kel(Scr)F,Vd(mean)

Method II = Predicted gentamicin concentration estimated by Kel(Scr)T,Vd(mean)

Method III = Predicted gentamicin concentration estimated by Kel(blood),Vd(mean)

Table 20B Measurement of relative performance for predicted peak and trough

Method	Trough				Peak			
	Bias Δme (CFDI)	statistic test	Precision Δmse (CFDI)	Statistic test	Bias Δme (CFDI)	statistic test	precision Δmse (CFDI)	statistic test
I VS II	0.9 (0.12,1.67)	S	3 (-3.93,9.93)	NS	0.93 (0.20,1.66)	S	5.57 (-4.45,15.59)	NS
I VS III	2.05 (0.03,4.07)	S	4.22 (-8.43,16.87)	NS	2.16 (0.09,4.22)	S	10.31 (-10.86,31.48)	NS
II VS III	1.15 (-0.18,2.48)	NS	1.32 (-4.49,7.13)	NS	1.23 (-0.19,2.65)	NS	4.74 (-6.58,16.06)	NS

CFDI = confidence interval

S = Significant (confidence interval did not include zero)

NS = No significant (confidence interval included zero)