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Predictability of Blood Levels of Gentamicin in Man

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Data from 42 patients were analyzed to determine the predictability of the peak serum level and the t½ of gentamicin on the bases of age, sex, body weight, serum concentration of creatinine, and blood hematocrit. Renal function was normal in 21 patients and impaired in 21. The most striking finding was the relatively poor predictability of t½ of gentamicin from serum concentration of creatinine. The overall correlation coefficient was 0.749 ($P < 0.001$) in contrast to values of >0.9 reported by others. There was a significant correlation of the t½ of gentamicin with the reciprocal of hematocrit ($r = 0.647$, $P < 0.001$). Linear regression equations taking account of sex, serum creatinine concentration, and reciprocal of hematocrit provided a somewhat higher correlation coefficient (0.821) with the t½ of gentamicin than did the equation including serum creatinine concentration alone but were still not fully satisfactory. Thus the pharmacokinetics of gentamicin may not be adequately predictable from standardized equations or nomograms.

A major problem in the use of gentamicin arises because of the narrow range between effective and toxic concentrations in serum. Although efficacy and toxicity appear to be influenced by factors other than serum concentration of the antibiotic, there is evidence that levels below 4 μg/ml are frequently insufficient for the treatment of serious infections due to *Pseudomonas* [1–4], while those in the range of 12–15 μg/ml may be associated with an increased risk of ototoxicity, especially in the presence of renal failure [3, 5, 6].

Gentamicin is eliminated from the body largely by renal glomerular filtration [7–9]. A small component of tubular secretion has also been postulated [10] but has not been substantiated [8]. The direct dependence of the excretion of gentamicin on renal function has led to the development of nomograms for determination of dosage for patients with renal insufficiency. These nomograms have been based on endogenous creatinine clearance [11–13] or serum creatinine concentration [14, 15] and have been reported to be highly predictive of the rate of clearance of the antibiotic.

During the past year we have had occasion to measure the serum levels of gentamicin in 42 patients at frequent intervals after the first dose of the drug. In this report we present our findings with respect to elimination kinetics and peak serum concentrations among these individuals, 21 of whom had normal renal function and 21 of whom had impaired renal function.

Materials and Methods

The patients studied were all those for whom serum assays of gentamicin were requested by the physician in charge of their cases at the New England Medical Center Hospital from July 1973 to April 1974. Of 42 individuals studied, 21 had normal renal function (serum creatinine, ≤1 mg/100 ml) and 21 had renal insufficiency (serum creatinine, >1 mg/100 ml). The patients were on the surgical, medical, and gynecological services. Many were receiving cephalothin or a penicillin in addition to gentamicin.

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Blood levels of gentamicin were measured after the first dose of drug in all instances. Blood was drawn 0.25, 0.5, 1, 3, 5, and 7 hr after the completion of iv infusions of gentamicin and 1, 3, 5, and 7 hr after im injection. Additional specimens were obtained from patients with renal insufficiency 11–48 hr after the drug was administered. The serum was stored at −20 C and assayed within 12–48 hr. All samples from a given patient were generally studied at the same time. The levels of creatinine in serum were determined by Auto Analyzer (SMA 6/60, Technicon Instruments, Tarrytown, N.Y.).

Assay method. A standardized spore suspension of *Bacillus subtilis* ATCC 6633 (approximately 3×10^8 organisms [1 ml]; Difc Laboratories, Detroit, Mich.) was added to 1 liter of molten trypticase soy agar (Baltimore Biological Laboratories, Baltimore, Md.) at 43 C. For the assay of specimens from patients receiving oxacillin, penicillin G, or ampicillin, two vials of penicillinase (Neutrapen,® Riker Laboratories, Northridge, Calif.) were added to the mixture; for patients receiving cephalothin, 10 mg of β-lactamase (provided by Eli Lilly, Indianapolis, Ind.) was added instead. The suspension was distributed in 10-ml aliquots into sterile petri dishes are permitted to harden. Filter-paper disks (6.35 mm in diameter, Schleicher and Schuell, Keene, N.H.) were briefly touched to the serum specimens until they were evenly moist and were placed on the surface of the agar. Standards were prepared in pooled human serum with gentamicin powder of known potency (Schering Corp., Kenilworth, N.J.) and were adsorbed onto filter paper disks. All samples were plated in triplicate. After the plates were incubated overnight at 37 C, zones of inhibition were measured. A standard curve was plotted on semilogarithmic paper, and specimens from the patients were assayed from this reference curve. The lower limit of sensitivity of the assay was approximately 0.4 μg/ml.

For examination of the accuracy of the assay technique, specimens of serum containing known concentrations of gentamicin were prepared and submitted under code for assay in the usual manner.

Pharmacokinetic calculations. Gentamicin levels in serum after im injection declined in a monoexponential fashion. Serum concentrations were plotted against time on semilogarithmic coordinates, and the first-order elimination rate constant (K) was determined from the slope of the linear least-squares regression line. The elimination t½ was then calculated according to the formula

$$t\tfrac{1}{2} = \frac{\ln 2}{K} = \frac{0.693}{K}.$$

Assuming that the im dose is rapidly absorbed [8, 15], one can calculate an apparent volume of distribution (AVD) from the extrapolated zero-time concentration (C_0) as follows:

$$AVD = \frac{dose}{C_0}.$$

Serum levels of gentamicin fluctuated markedly during the first hour after iv infusion. Accordingly, K or t½ was obtained from subsequent values. Since the exact infusion rate was not known and serum samples were not obtained during infusion, an AVD could not be calculated for patients who received gentamicin iv.

Results

The precision of the assay was assessed on the basis of 27 samples prepared to contain 1.7–10 μg of gentamicin/ml. The correlation of the prepared concentration with the assayed concentration was 0.92 ($P < 0.001$). The slope of the regression line (1.03) was not significantly different from 1.00 ($P > 0.95$), and the intercept (−0.16) was not significantly different from 0 ($P > 0.70$). Approximately two-thirds of the patients in both groups (normal and abnormal renal function) were receiving penicillin G, ampicillin, oxacillin, or cephalothin. The enzymes incorporated into the agar were able to destroy >5,000 μg of penicillin G, ampicillin, or oxacillin/ml and >1,000 μg of cephalothin/ml. These enzymes had no effect on the assay of gentamicin.

The seven males and 14 females with normal renal function ranged in age from 17 to 74 years (median, 45 years) and weighed 45–100 kg (median, 62 kg). Although values for blood urea nitrogen (BUN) were slightly elevated in three of these individuals, their serum creatinine measurements remained consistently ≤1.0 mg/100

ml. Three individuals (patients no. 5, 9, and 17) had elevated serum bilirubin values of 16–33 mg/100 ml. Serum albumin was measured in nine patients with normal renal function; the mean ±SE of the values was 3.1 ± 0.1 (range, 2.1–4.1) g/100 ml. Albumin concentrations were determined in sera of 17 patients with renal impairment; the mean ± SE of the values was 2.9 ± 0.1 (range, 2.1–3.8) g/100 ml. No individual was in clinical shock, and in only one instance was there a striking derangement of fluid or electrolyte balance (patient no. 42, who was grossly edematous). Renal function was relatively stable except in four individuals. In two of these four patients (no. 27 and 38), the serum level of creatinine was rising rapidly as a result of acute renal failure; in the others (patients no. 25 and 32), the values were declining because of hemodialysis. In no instance were the kinetics of gentamicin measured during dialysis.

Peak serum levels. Twenty-three patients received gentamicin iv or im in the commonly used dose range of 1.2–1.7 mg/kg. Of these patients, 20 exhibited peak serum levels of <5 μg/ml, and values for 15 of these patients were <4 μg/ml. The overall range was 1.6–7.4 μg/ml. The rate of iv administration of gentamicin fluctuated because infusion pumps were not used. Therefore, the relation between peak serum level and dose of drug was analyzed only for patients receiving im injections. The peak serum level correlated as well with the total quantity of drug administered (mg) as with the dose on a weight basis (mg/kg).

In figure 1, peak serum levels have been plotted against dose of gentamicin. The relation between these variables was similar in patients with normal renal function and in those with abnormal renal function; thus data for the two groups have been pooled. The results for two patients have been omitted. One individual (patient no. 13) weighed 45 kg, received a dose of 3.5 mg/kg, and exhibited a peak level of 17 μg/ml; the other patient (no. 2) weighed 100 kg, received 2.5 mg of drug/kg, and had a peak serum level of 4.8 μg/ml. As is shown in figure 1, the peak serum levels produced by a given dose varied considerably among patients. The slope of the least-squares regression line through the origin was 0.0448 μg/ml/mg or 4.48 μg/ml/100 mg. The correlation

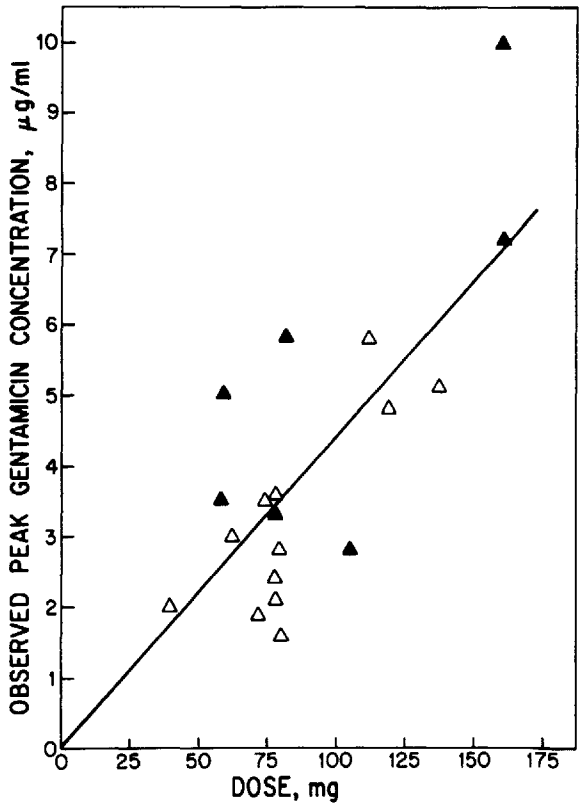

Figure 1. Relation between the observed peak concentration of gentamicin and the im dose for patients with normal renal function (Δ) and those with impaired renal function (▲). The solid line represents the least-squares regression line through the origin.

coefficient was 0.762 ($P < 0.001$). There was no apparent relation between the peak level of drug and the blood hematocrit.

Pharmacokinetic measurements. These results, together with data on blood chemistry of patients with normal and impaired renal function, are presented in tables 1 and 2. The mean ±SE of the elimination constant for the 21 patients with normal renal function was 0.264 ± 0.03; the t½ of gentamicin in these individuals was 3.12 ± 0.27 hr. Simple and multiple regression analyses were performed with data from all 42 individuals for study of the dependence of the t½ of gentamicin on various patient characteristics and biochemical indices of renal function.

Simple linear regression. (1) Serum creatinine. Theoretical considerations suggest that the elimination t½ of drugs that are exclusively excreted by glomerular filtration should be

Table 1. Clinical and pharmacokinetic data for patients with normal renal function.

Route of administration, patient no.	Age in years (sex)	Weight (kg)	Creatinine (mg/100 ml)	BUN (mg/100 ml)	Hematocrit (%)	Gentamicin					
						Dose (mg)	Peak serum level (μg/ml)	K (hr^{-1})	t½ (hr)	AVD Liters	AVD % of body weight
im											
1	38 (F)	55	0.7	13	42	140	5.1	0.223	3.10	25.3	46.1
2	43 (F)	100	1.0	14	35	250	4.8	0.169	4.11	41.4	41.4
3	65 (F)	70	1.0	40	33	120	4.8	0.233	2.97	18.3	26.2
4	46 (F)	71	0.8	11	37	80	3.6	0.268	2.59	15.0	21.1
5	45 (F)	83	1.0	6	28	80	3.5	0.402	1.72	15.6	18.8
6	43 (F)	52	0.7	14	33	60	3.0	0.334	2.08	15.0	28.8
7	30 (F)	46	0.6	14	34	80	2.5	0.718	0.97	18.2	39.5
8	18 (M)	79	0.8	19	41	40	2.0	0.402	1.72	10.9	13.8
9	61 (M)	80	1.0	11	42	70	1.9	0.216	3.20	30.9	38.5
10	29 (M)	71	0.8	15	48	75	2.4	0.173	4.02	27.4	38.6
11	55 (F)	53	0.7	11	41	80	2.8	0.145	4.77	22.3	42.1
12	45 (F)	70	0.8	13	32	120	5.8	0.139	4.97	17.1	24.4
13	53 (F)	45	1.0	13	35	160	17.0	0.278	2.49	7.3	16.2
14	70 (F)	50	0.7	11	31	80	1.6	0.232	2.99	35.0	70.0
iv											
15	53 (M)	62	1.0	18	24	80	5.4	0.112	6.20	...	...
16	21 (F)	52	1.0	10	45	80	4.2	0.228	3.05	...	...
17	70 (M)	50	0.8	15	30	65	2.0	0.239	2.90	...	...
18	74 (M)	90	1.0	30	34	150	3.7	0.202	3.44	...	...
19	30 (F)	47	0.6	29	33	80	3.8	0.426	1.63	...	...
20	18 (F)	62	0.9	21	34	80	4.5	0.192	3.61	...	...
21	17 (M)	61	1.0	14	45	80	4.0	0.223	3.10	...	...

NOTE. BUN = blood urea nitrogen; K = elimination rate constant; t½ = half-life; AVD = apparent volume of distribution.

directly proportional to the serum concentration of creatinine [16]. The t½ of gentamicin is plotted against the serum concentration of creatinine in figure 2. A simple linear least-squares regression of t½ on serum creatinine concentration yielded a correlation coefficient (r) of 0.7499 ($P < 0.001$). The square of the correlation coefficient (r^2), sometimes referred to as the coefficient of determination, when multiplied by 100 provides the percentage of total variance of the dependent variable (i.e., t½) that can be attributed to its linear regression on the chosen independent variable (i.e., serum creatinine). In the present instance 100 r^2 was calculated to be 56.2%. Thus little more than half of the variance of the t½ of gentamicin can be accounted for by serum creatinine alone.

For predictive purposes, a regression equation relating the t½ of gentamicin to the serum concentration of creatinine is required. Because the various laboratory measurements involved are subject to error, both t½ and serum creatinine concentration should be treated as random variables. When the least-squares regression analysis is a bivariate one, the best functional relationship between the two variables is described by the orthogonal regression line [17]. Such a regression line for the correlation between the t½ of gentamicin and the serum concentration of creatinine is included in figure 2. The equation for this line is:

$$t½ = 0.224 + 2.15\ (Cr),$$

where serum creatinine concentration (Cr) is expressed in mg/100 ml. As expected from theory [16], the intercept is not significantly different from 0. It follows that the t½ of gentamicin can be roughly approximated by multiplying the serum creatinine concentration by 2.

(2) BUN. The linear regression coefficient between the t½ of gentamicin and the BUN was 0.5028. Although this value is statistically sig-

Table 2. Clinical and pharmacokinetic data for patients with impaired renal function.

Route of administration, patient no.	Age in years (sex)	Weight (kg)	Creatinine (mg/100 ml)	BUN (mg/100 ml)	Hemato-crit (%)	Gentamicin					
						Dose (mg)	Peak serum level (μg/ml)	K (hr^{-1})	t½ (hr)	AVD Liters	AVD % of body weight
im											
22	47 (F)	65	1.7	26	39	80	3.3	0.160	4.3	20.4	31.4
23	76 (M)	63	2.2	41	38	80	5.8	0.423	1.6	8.1	12.9
24	19 (F)	37	2.7	67	29	60	5.0	0.204	3.3	9.9	26.8
25	23 (M)	64	3.8	26	21	60	3.5	0.108	6.3	16.4	25.7
26	41 (M)	75	6.8	72	20	105	2.8	0.040	17.2	37.8	50.4
27	63 (M)	70	7.0	98	25	160	7.2	0.056	12.4	31.5	45.0
28	40 (M)	80	14.8	201	33	160	10.0	0.036	19.1	18.8	23.5
iv											
29	69 (M)	60	1.7	34	27	80	2.9	0.245	2.8	...	...
30	60 (M)	75	2.0	30	21	60	1.8	0.053	13.1	...	...
31	73 (M)	59	2.4	28	46	80	4.2	0.219	3.1	...	...
32	48 (F)	45	2.5	> 200	21	80	4.0	0.065	10.6	...	...
33	55 (F)	61	2.7	14	27	80	7.4	0.151	4.6	...	...
34	58 (M)	85	3.3	123	35	210	13.0	0.123	5.6	...	...
35	70 (M)	50	4.5	85	28	125	7.2	0.027	25.8	...	...
36	70 (M)	70	4.5	123	34	140	5.8	0.131	5.2	...	...
37	65 (M)	55	4.7	75	34	80	3.7	0.228	3.0	...	...
38	27 (F)	53	6.1	111	24	80	3.8	0.156	4.4	...	...
39	70 (F)	55	8.4	91	24	60	3.1	0.112	6.2	...	...
40	54 (M)	61	8.8	37	17	150	6.4	0.025	27.9	...	...
41	63 (M)	83	11.8	132	30	200	9.6	0.040	17.4	...	...
42	54 (M)	70	15.0	88	18	160	6.3	0.033	20.8	...	...

NOTE. Patients are arranged in order of increasing serum concentrations of creatinine. BUN = blood urea nitrogen; K = elimination rate constant; t½ = half-life; AVD = apparent volume of distribution.

nificant ($P < 0.001$), it is obviously too low to have any predictive value.

(3) Blood hematocrit. Most of the patients with renal impairment, but only two of 21 patients with normal renal function, had hematocrit levels below 30% (tables 1 and 2). A curvilinear relationship appeared to exist between hematocrit and the t½ of gentamicin in individual patients (figure 3). The data, however, could be reasonably linearized by a plot of t½ against the reciprocal of hematocrit. A bivariate linear least-squares fit of the data yielded the following equation:

$$t½ = -30.3 + \frac{1.11 \times 10^3}{(\%\ \text{hematocrit})}.$$

A correlation coefficient of 0.6477 ($P < 0.001$) was obtained. Thus, the simple regression on the reciprocal of hematocrit accounted for 42% of the total variance of the t½ of gentamicin. The level of predictability achieved with hematocrit was intermediate between that found with serum creatinine and that found with BUN.

Multiple linear regression. Thus far we have presented individual correlations of t½ with serum concentration of creatinine, BUN, and hematocrit. By simultaneous regression of the t½ of gentamicin against all three parameters, more of the total variance could conceivably be explained. Moreover, endogenous creatinine clearance and serum creatinine concentrations are known to be dependent on sex [16], age, and body weight [18, 19], and differences in these three characteristics may have a direct effect on the elimination of gentamicin. Since sex is not a continuous variable, a "dummy" representation with a value of 0 for male and 1 for female was assigned [20]. A multiple linear regression[1] was

[1] The multiple regression program, BMD03R, is one of several Bio-Medical Computer Programs, adapted for use at the State University of New York at Buffalo, from the

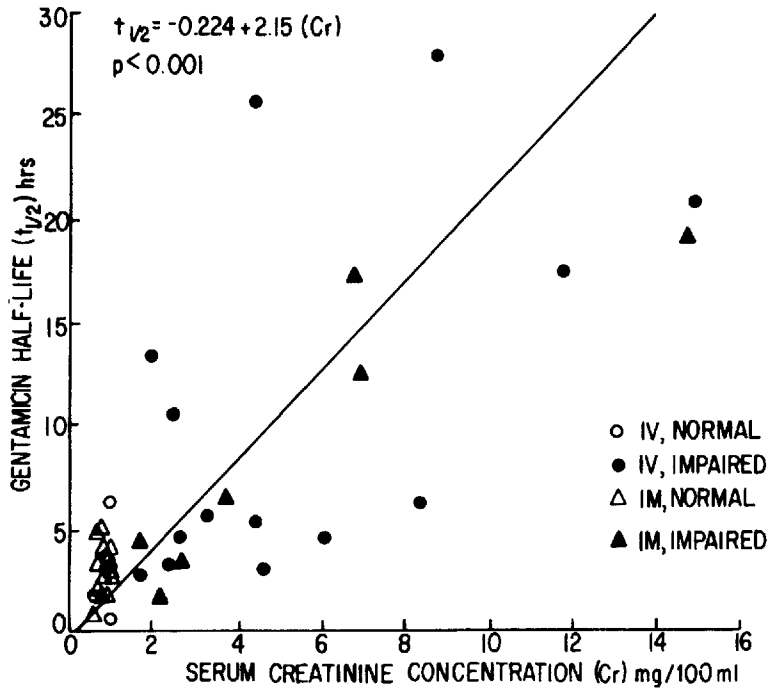

Figure 2. Relation of serum half-life of gentamicin to serum concentration of creatinine (Cr) in 42 patients with normal or impaired renal function. Solid line is the bivariate linear least-squares regression line.

then performed on a CDC 6400 digital computer. The dependent variable was the t½, and the input independent variables included sex, age, body weight, serum creatinine concentration, BUN, and reciprocal of hematocrit. As is shown in table 3, the multiple correlation coefficient for all six parameters was 0.8212. When the regression coefficients for each of the six variables were examined, only those for serum creatinine concentration and the reciprocal of hematocrit reached an acceptable level of statistical significance. (The regression coefficient for sex was of borderline significance, and its interpretation was obscured by the uneven distribution of males and females in the two groups of patients.)

The importance of the individual variables in explanation of the total variance is also expressed by the partial correlation coefficients, which are the computed correlations between t½ and each of the variables when the remaining ones are held at fixed values. The deletion of age, body weight, and BUN from the regression caused no reduction in the strength of correlation or predictability. Accordingly, one can write a linear regression equation solely in terms of sex, serum creatinine concentration, and reciprocal of hematocrit. For males the t½ of gentamicin is obtained by the following equation:

$$t½ = -3.68 + 0.898\ (Cr) + \frac{2.58 \times 10^2}{(\%\ \text{hematocrit})}.$$

For females the following equation was used:

$$t½ = -5.02 + 0.898\ (Cr) + \frac{2.58 \times 10^2}{(\%\ \text{hematocrit})}.$$

In each equation, serum creatinine concentration is expressed as mg/100 ml.

Evaluation of creatinine clearance. Siersbaek-Nielsen et al. [19] have provided a nomogram by means of which creatinine clearance can be computed from the serum level of creatinine alone. In effect, the nomogram corrects for changes due to sex, age, and body weight in the relation between serum creatinine and its clearance. A similar approach was used by Nielsen et al. [21] for calculation of the t½ of kanamycin. We therefore used Siersbaek-Nielsen's nomogram to convert all values for serum concentrations of creatinine into clearance values. The elimination rate constant (K) of gentamicin for the 42 patients studied was plotted

Health Sciences Computer Facility, Department of Preventive Medicine and Public Health, School of Medicine, University of Los Angeles, Los Angeles, Calif.

Table 3. Results of multiple linear regression analysis of t½ of gentamicin in 42 patients.

Independent variables	Regression coefficient (SE)	*t* value (df = 35)	Partial correlation coefficient
Sex*	−2.31 (1.53)	−1.512 †	−0.248
Age (years)	4.73×10^{-3} (3.85×10^{-2})	0.123 ‡	0.021
Weight (kg)	-3.08×10^{-3} (5.18×10^{-2})	−0.059 ‡	−0.010
Serum creatinine concentration (mg/100 ml)	0.898 (0.286)	3.139 §	0.469
Blood urea nitrogen (mg/100 ml)	1.1×10^{-4} (1.82×10^{-2})	0.006 ‡	0.001
Reciprocal of hematocrit	2.56 (0.845)	3.036 §	0.457

NOTE. The overall statistics are as follows: intercept = −3.69 hr; SE of estimate = 4.18 hr; coefficient of determination = 0.6744; multiple correlation coefficient = 0.8212; df = degrees of freedom.

* "Dummy" variable: male = 0, female = 1.

† $0.2 > P > 0.1$.

‡ $P > 0.2$.

§ $0.005 > P > 0.001$.

against the estimated rate of creatinine clearance (figure 4). The points exhibited considerable scatter. In addition, there did not appear to be a clear linear dependence of K on the rate of creatinine clearance; such a dependence was suggested by theory [22]. Instead, most patients with creatinine clearance values above 60 ml/min had nearly normal K values for gentamicin.

Apparent volume of distribution (AVD). Considerable variation in the AVD was noted from one individual to another (see tables 1 and 2). Patient no. 14 had an unusually large AVD (i.e., 70% of her body weight). Except for this individual, the AVD in terms of percentage of body weight varied over a fourfold range (12%–50%). The mean values for patients with normal renal function were not significantly different from those for patients with impaired

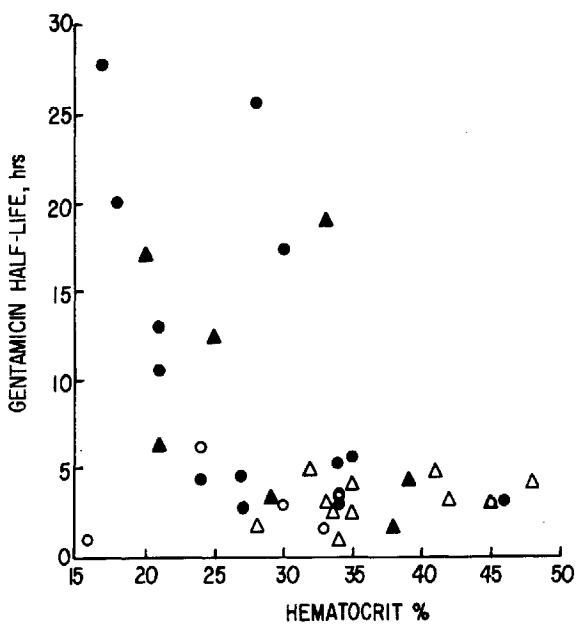

Figure 3. Relation of serum half-life of gentamicin to hematocrit in 42 patients with impaired (closed symbols) or normal (open symbols) renal function. Circles indicate iv administration; triangles indicate im administration.

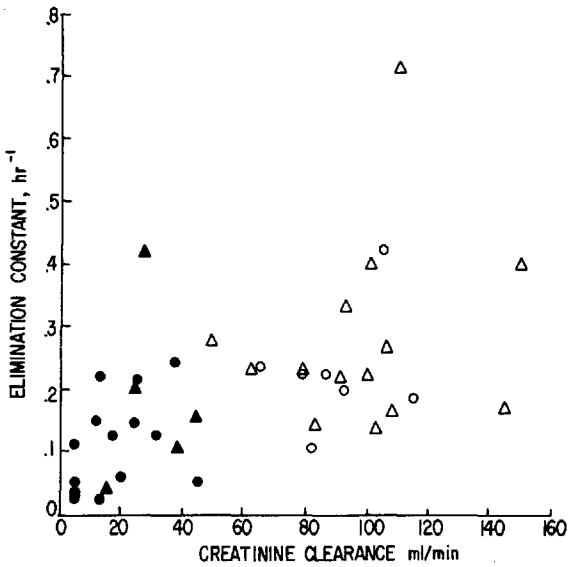

Figure 4. The elimination rate constant of gentamicin plotted as a function of endogenous creatinine clearance. Values were estimated from serum concentration of creatinine in 42 patients according to the nomogram of Siersbaek-Nielsen et al. [19]. Closed symbols indicated impaired renal function; open symbols indicate normal renal function. Circles indicate iv administration; triangles indicate im administration.

Table 4. Comparison of apparent volume of distribution (AVD) in 14 patients with normal renal function with that in seven patients with impaired renal function.

	AVD		
Renal function	Liters	% of body weight	
Normal	21.4 ± 9.6	33.2 ± 15.0	$P > 0.7$
	$P > 0.8$	$P > 0.8$	
Impaired	20.4 ± 10.8	30.8 ± 12.9	
Total	21.1 ± 9.7	32.4 ± 14.1	

NOTE. Values are means ± SD.

renal function by the *t*-test (table 4). The overall AVD was 21.1 liters, or 32.4% of body weight. The AVD did not appear to be related to body weight, since linear regression of the two functions yielded a least-squares regression slope that was not significantly different from 0 ($P > 0.1$).

Discussion

Optimal therapy of serious infections due to *Pseudomonas aeruginosa* with gentamicin appears to require the production of peak serum levels of 5–8 μg/ml [2–4]. While the determinants of ototoxicity and nephrotoxicity due to this agent are not clear [3, 6, 23], it is generally thought that blood levels above 10–12 μg/ml should be avoided [3]. A variety of approaches have been devised for prediction of the t½ of gentamicin in serum, particularly in patients with impaired renal function, and for production of peak serum levels in the range of 4–10 μg/ml. Equations and nomograms based on the rate of endogenous creatinine clearance [11–13] or on serum creatinine concentration [14, 15] have been stated to correlate well with the observed rate of clearance of gentamicin.

The present report is an analysis of our experience concerning the predictability of peak serum levels and t½ of gentamicin based on the use of common parameters. As is usually the practice in this institution, the rates of creatinine clearance were not determined, and the concentration of creatinine in serum was used as a guide for the degree of renal impairment. Marked differences were noted in sex distribution and route of administration between patients with normal renal function and those with impaired renal function. These disparities arose by chance; nevertheless, they may have affected our results. The method used for assay of gentamicin appears to have been acceptably accurate, and recent data indicate that the presence of hyperbilirubinemia in three individuals probably did not affect the assay [24].

Doses of gentamicin in the commonly used range of 1.2–1.7 mg/kg (iv or im) produced peak serum levels of ≤5 μg/ml in 20 of 24 recipients; in 15 of these patients, the peak was <4 μg/ml. It may be presumed that specimens obtained earlier than 15 min after completion of the iv infusion would have yielded somewhat higher concentrations. Marked variations among patients were observed in the maximal serum level produced by a given dose of drug, a finding noted by others [4, 14, 25–27].

The peak serum concentration of gentamicin measured after im injection correlated as well with the total quantity of drug given (mg) as with the dose in mg/kg. The correlation coefficient between dose (mg) and peak serum level was 0.762; this value is similar to that reported by Kaye et al. ($r = 0.79$) for peak serum level vs. dose in mg/kg [27]. It is possible that the computation of dose on the basis of lean body mass would result in greater predictability of the values.

Riff and Jackson noted a significant inverse correlation between peak levels of gentamicin and hematocrit in adults [25]. Such a relation was not evident in several studies of infants [28–30] or in our own population. However, the finding in the present study of a significant inverse correlation between hematocrit and t½ of gentamicin suggests that a relation similar to that noted by Riff and Jackson might have become evident had our patients been studied after multiple doses.

The mean t½ of gentamicin in our patients with normal renal function (3.12 hr) was in the range usually reported [8, 14, 15, 31, 32]. There was considerable variation from one individual to another, as has been noted by others [3, 4, 27, 31]. Riff and Jackson characterized the patterns of response as "accelerated," "typical," or "dampened." These patterns were reproducible within an individual and were unrelated to the route of administration, associated diseases, age, sex, or weight [25].

A particularly striking finding in the present

study was the fact that the correlation coefficient between t½ of gentamicin and serum creatinine concentration was only 0.749, in contrast to values of >0.9 reported by Cutler et al. [15] and McHenry et al. [14]. However, Kaye et al., in a compilation of their own results with those of four other groups, observed a similarly poor correlation coefficient ($r = 0.71$) between the rates of clearance of gentamicin and creatinine [27]. An extremely poor correlation between these two variables was also noted by McCracken among infants two to 24 months of age [28]. The proportionality factor relating serum creatinine concentration (mg/100 ml) to t½ of gentamicin in the present study was 2.15. This value is lower than the values found by others (3–4) [14, 15].

There was a significant correlation between the reciprocal of hematocrit and the t½ of gentamicin in the present investigation. Such a relation was not evident in a pediatric study [29]. Although anemia is extremely common in patients with impaired renal function, multiple linear regression analysis suggested that the effect of hematocrit could not be explained simply as a manifestation of azotemia, but rather that this variable contributed separately to the pharmacokinetics of gentamicin. There was no apparent relation between the t½ of gentamicin and the level of serum albumin or between the hematocrit and the AVD.

The curvilinear relation observed between the elimination constant of gentamicin and the estimated rate of creatinine clearance in the present study (figure 4) is surprising since the drug appears to fulfill the criteria of exclusive glomerular filtration [7–9]. A similar curvilinear relation was reported by Chan et al., who noted that patients with creatinine clearance values above 70 ml/min/1.73 m^2 of body surface area had normal elimination rate constants for gentamicin [13]. These findings raise doubt as to the validity of assuming a linear relation between the elimination rate constant of gentamicin and creatinine clearance over the entire clinical range.

It has been suggested that, because of its molecular size and minimal binding to plasma protein [7, 8, 33], gentamicin is freely diffusible in the interstitial tissue water. This hypothesis is supported by the fact that the AVD of gentamicin is similar to that of extracellular body water. The AVD estimated in our patients varied considerably from one individual to another, although the average value is in accord with data reported by others [7, 8]. We found, as did Gyselynck et al. [7], that the AVD is not dependent on body weight. In contrast to those authors, however, we noted no significant difference between values in patients with normal renal function and values in those with impaired renal function.

The data in the present study indicate that the predictability of the t½ of gentamicin on the bases of sex, age, body weight, serum creatinine, BUN, and hematocrit in patients with renal impairment is far from satisfactory. Using all of the clinical and laboratory information, we could, at best, account for only two-thirds of the total variance of t½ of gentamicin. The obvious implication is that, in patients with serious infections and compromised renal function, serum levels of gentamicin should be monitored frequently so that adjustments can be made for individual variations in the rate of clearance of the antibiotic. In practice, specimens might be obtained at the time of the peak serum level (e.g., immediately after iv infusion and about 1 hr after im injection) and just before the next dose of drug on the first day of therapy and every few days thereafter.

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