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Pharmacokinetics of Dosing Regimens Which Utilize Multiple Intravenous Infusions: Gentamicin in Burn Patients

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A general approach to the establishment of dosing regimens for drug administration by multiple intravenous infusions is presented. The method is applicable where the elimination kinetics are first order and can be represented by a one-compartment open model. The approach utilizes serum concentration–time data obtained during any dosing interval for the calculation of the apparent distribution volume and the half-life in individual patients. These values are then used to individualize the dosing regimen where it is required to maintain serum concentrations of the drug within a desired range. Estimation of kinetic parameters for gentamicin in burn patients with normal or only slightly reduced renal function demonstrates a relatively constant distribution volume of 0.25 ± 0.086 liter/kg (mean ± SD) but a relatively variable half-life of 2.1 ± 1.3 hr. This finding supports the view that gentamicin regimens should be individualized even in patients with essentially normal renal function.

KEY WORDS: dosage regimens; multiple infusions; maximum and minimum serum concentrations; gentamicin kinetics in burn patients.

INTRODUCTION

The administration of certain drugs by multiple intravenous infusion is commonly employed in hospitalized patients. A number of antibiotics, including the aminoglycosides, are often given by this route. Agents which cannot be given orally because of poor absorption characteristics or short half-lived drugs whose serum or plasma concentrations must be maintained within a narrow therapeutic range are candidates for this mode of administration.

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Administration by multiple constant-rate infusions rather than by multiple intravenous boluses presents an inconvenience in that infusion rates controlled by gravity drip or by infusion pump must be monitored over the infusion interval. However, because this mode results in a smaller range of peak to trough serum concentrations for a given regimen it may be preferred where it is desirable to maintain drug concentrations in a narrow therapeutic range.

Studies have indicated that the half-life of the aminoglycoside antibiotic gentamicin is quite variable, even in patients with normal renal function (1,2). Since this drug also has a low therapeutic index, the need for individualizing gentamicin dosing regimens seems clear. The ototoxic effects of this antibiotic appear to be associated with serum concentrations higher than 12 mg/liter (3). Peak serum concentrations during multiple dose administration should therefore be kept below this level. To ensure adequate therapy, peak levels must at least surpass the minimum effective serum concentration for the infecting organism. On the other hand, the need for maintaining a desired minimum serum concentration of gentamicin is not clear. It has been suggested that the incidence of nephrotoxicity may be increased when serum concentrations higher than 2 mg/liter are maintained during prolonged therapy (4).

Some authors have suggested methods for establishing gentamicin dosing regimens based on measured parameters of renal function (1,5–8). The approach presented here can be applied even in patients with normal renal function. It is used first to obtain direct estimates of the individual patient's kinetic parameters. Second, the method allows the estimation of dosing intervals and infusion rates required to produce desired maximum and/or minimum serum concentrations. The latter calculations are based on the estimated half-lives and distribution volumes, and on the choice of a convenient infusion period. The approach is generally applicable where plasma concentrations of drug can be measured during any infusion interval in a series of constant-rate infusions.

THEORETICAL

Estimation of V_d and $t_{1/2}$ from Serum Concentration–Time Data Obtained During the Postinfusion Phase

Assuming first-order elimination of drug in the one-compartment model shown in Fig. 1, the equation which describes the change in plasma or serum concentration, C_p, during constant-rate infusion is

$$dC_p/dt = k_0/V_d - k_d C_p \tag{1}$$

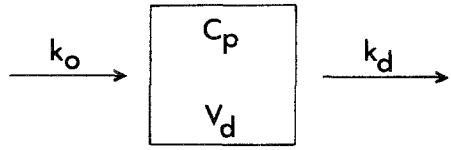

Fig. 1. One-compartment model with zero-order infusion and first-order drug elimination.

where k_0 is the zero-order infusion rate, V_d is the apparent distribution volume, and k_d is the first-order elimination rate constant.

At the end of any infusion period in a series of multiple intravenous infusions (whether or not at steady state), the serum concentration, $C_{p_{max}}$, is given by

$$C_{p_{max}} = (k_0/k_d V_d)(1 - e^{-k_d t'}) + C_{p_0} e^{-k_d t'} \tag{2}$$

where t' is the duration of the infusion and C_{p_0} is the concentration in serum remaining from a previously administered dose. Rearrangement of equation 2 yields

$$V_d = \frac{k_0}{k_d} \frac{(1 - e^{-k_d t'})}{(C_{p_{max}} - C_{p_0} e^{-k_d t'})} \tag{3}$$

The serum concentration during the postinfusion phase is

$$C_{p_{post}} = C_{p_{max}} e^{-k_d (t - t')} \tag{4}$$

where t is time taken from the beginning of that infusion.

Serum concentration–time data obtained during the postinfusion phase can thus be fitted to equation 4, giving estimates of k_d (or $t_{1/2}$) and $C_{p_{max}}$. These values can then be used to estimate the apparent distribution volume in equation 3. If data from other than the first infusion interval are used, the preinfusion level (C_{p_0}) must also be known. If the subject is at steady state, however, an estimate of this preinfusion level can be made by the serum concentration measured (or predicted by equation 4) at the end of the infusion interval.

Possible Error in Estimation of Peak Serum Concentration Where Drug Elimination During the Infusion Period Is Neglected

Where the half-life of the administered drug is long relative to the infusion period (i.e., multiple intravenous boluses rather than infusions are administered), the increase in plasma or serum concentration (ΔC_{p^*}) of drug during any infusion period may be approximated as

$$\Delta C_{p^*} = k_0 t'/V_d \tag{5}$$

The peak serum concentration produced on termination of the initial infusion is similarly approximated as

$$C_{p_{\max_{t'}}^{*}} = k_0 t'/V_d \tag{6}$$

A more accurate estimate of the peak serum concentration takes into account the elimination of drug during the first infusion period, and thus

$$C_{p_{\max_{t'}}} = (k_0/k_d V_d)(1 - e^{-k_d t'}) \tag{7}$$

where $t_{1/2} = nt'$, i.e., n is the ratio of half-life to infusion time,

$$C_{p_{\max_{t'}}} = (1.44 n t' k_0/V_d)(1 - e^{-0.693/n}) \tag{8}$$

and

$$\frac{C_{p_{\max_{t'}}^{*}}}{C_{p_{\max_{t'}}}} = \frac{0.693}{n(1 - e^{-0.693/n})} \tag{9}$$

Thus the percent relative error in estimating the peak serum concentration during the first infusion phase by equation 6 is

$$\text{Percent relative error} = 100\left(\frac{0.693}{n(1 - e^{-0.693/n})} - 1\right) \tag{10}$$

The relative error in this estimation is tabulated for various values of n in Table I.

Calculation of Infusion Rates for Administration by Multiple Intravenous Infusions

Where multiple constant-rate infusions are administered for a fixed infusion period t', at fixed intervals, τ, the infusion rate required to produce a desired maximum and/or minimum serum concentration at steady state is calculated as follows:

Table I. Error in Estimation of Peak Serum Concentration During the First Infusion Period Assuming Negligible Drug Elimination During the Period ($n = t_{1/2}/t'$)

n	Percent relative error
1	38.6
2	18.3
4	8.9
8	4.4
16	2.2
32	1.1

Case 1: *Required to Achieve a Desired* $C_{p_{max_\infty}}$

The serum concentration at the end of any infusion period as defined in equation 2 is

$$C_{p_{max}} = (k_0/k_d V_d)(1 - e^{-k_d t'}) + C_{p_o} e^{-k_d t'} \tag{11}$$

The serum concentration at the end of the infusion interval (i.e., at the beginning of the next infusion interval) is

$$C_{p_{min}} = C_{p_{max}} e^{-k_d(\tau - t')} \tag{12}$$

where $\tau - t'$ is the length of the postinfusion phase (Fig. 2).

At steady state, the concentration at the beginning of the infusion period is

$$C_{p_0} = C_{p_{min_\infty}} = C_{p_{max_\infty}} e^{-k_d(\tau - t')} \tag{13}$$

and thus equation 11 under steady-state conditions becomes

$$C_{p_{max_\infty}} = (k_0/k_d V_d)(1 - e^{-k_d t'}) + C_{p_{max_\infty}} e^{-k_d \tau} \tag{14}$$

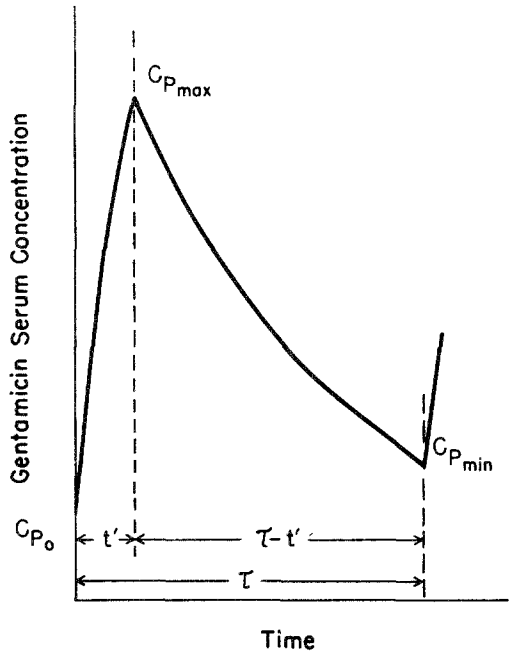

Fig. 2. Serum concentration–time profile for gentamicin during an infusion interval prior to the attainment of steady state. The dosing interval, τ, is composed of an infusion period, t', and a postinfusion phase, $\tau - t'$.

and therefore

$$C_{p_{\max_\infty}} = \frac{k_0(1 - e^{-k_d t'})}{k_d V_d(1 - e^{-k_d \tau})} \tag{15}$$

The infusion rate required to produce the desired $C_{p_{\max_\infty}}$ is obtained by rearrangement of equation 15 to give

$$k_0 = k_d V_d C_{p_{\max_\infty}} \frac{(1 - e^{-k_d \tau})}{(1 - e^{-k_d t'})} \tag{16}$$

Case 2: Required to Achieve a Desired $C_{p_{\min_\infty}}$

If it is desirable to maintain concentrations above some minimum therapeutic level during the administration of multiple infusions, $C_{p_{\min_\infty}}$ can be calculated as follows, once values for τ and t' have been chosen. From equations 13 and 15,

$$\begin{aligned} C_{p_{\min_\infty}} &= \frac{k_0(1 - e^{-k_d t'})\, e^{-k_d(\tau - t')}}{k_d V_d(1 - e^{-k_d \tau})} \\ &= \frac{k_0}{k_d V_d} \frac{(e^{k_d t'} - 1)}{(e^{k_d \tau} - 1)} \end{aligned} \tag{17}$$

The infusion rate required to produce the desired $C_{p_{\min_\infty}}$ is then obtained by rearrangement of equation 17, to give

$$k_0 = k_d V_d C_{p_{\min_\infty}} \frac{(e^{k_d \tau} - 1)}{(e^{k_d t'} - 1)} \tag{18}$$

Case 3: Required to Maintain Steady-State Serum Concentrations Within a Desired Range

Where it is desired to maintain the steady-state serum concentrations of drug within a certain range, this can be achieved by first selecting a convenient infusion period t' and then calculating the required infusion interval based on the estimated half-life of the drug. The postinfusion phase is obtained from the desired ratio of $C_{p_{\min_\infty}}/C_{p_{\max_\infty}}$ as

$$\tau - t' = \frac{-1}{k_d} \ln \left[\frac{C_{p_{\min_\infty}}}{C_{p_{\max_\infty}}} \right] \tag{19}$$

or from the nomogram in Fig. 3. The dosing interval τ is then calculated as the sum of the infusion and postinfusion phases.

The infusion rate required to produce the desired $C_{p_{\max_\infty}}$ or $C_{p_{\min_\infty}}$ is calculated from equation 16 or 18, respectively, using the selected infusion period and the calculated dosing interval.

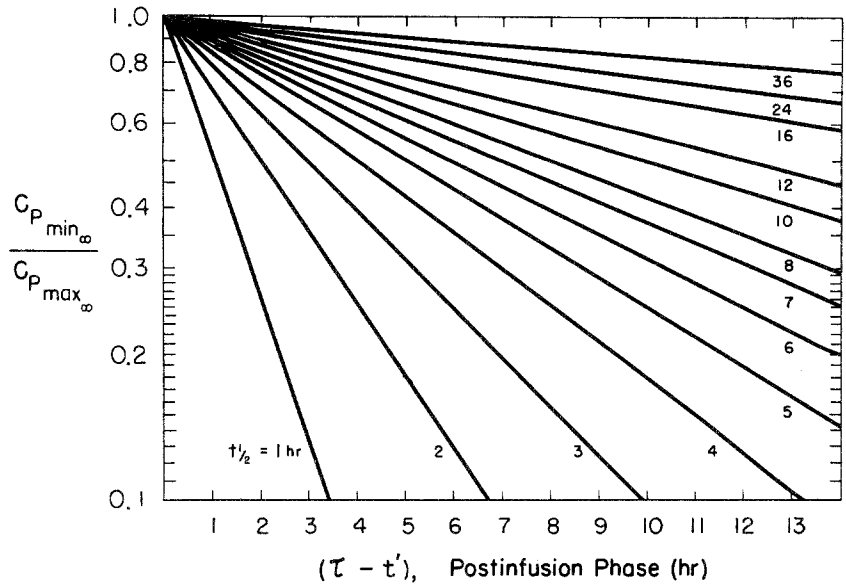

Fig. 3. Nomogram for estimation of duration of postinfusion phase as in function of drug half-life. The nomogram can be used to obtain a desired ratio of $C_{p_{min_\infty}}/C_{p_{max_\infty}}$ by selection of an appropriate postinfusion phase.

Example Calculation for Case 3

A 60-kg patient received a 1-hr infusion of gentamicin. Analysis of the postinfusion serum concentration–time data yields an estimated half-life of 2.7 hr and a volume of distribution of 0.21 liter/kg. The desired maximum and minimum steady-state serum concentrations for this patient are 6.0 and 1.0 mg/liter, respectively. The postinfusion phase is estimated from equation 19 as

$$\tau - t' = -1.44 \times 2.7\,\text{hr} \times \ln 0.167$$

$$= 6.96\,\text{hr}$$

Since an infusion period of 1 hr is chosen, the dosing interval, τ, is 7.96 hr.

Rounding the dosing interval to 8 hr, the required infusion rate is calculated from equation 16 as

$$k_0 = \frac{(0.693/2.7\,\text{hr})(12.6\,\text{liters})(6\,\text{mg/liter})(1 - e^{-2.05})}{(1 - e^{-0.257})}$$

$$= 74.7\,\text{mg/hr}$$

A regimen of 75 mg infused over 1 hr at 8-hr intervals will thus provide a steady-state maximum serum concentration equal to 6 mg/liter and a minimum of approximately 1 mg/liter in this example.

EXPERIMENTAL

Patients

Eleven patients suffering from extensive body burns were included in this study (Table II). The patients were hospitalized in the Burn Unit at St. Paul-Ramsey Hospital and Medical Center. All were receiving gentamicin by multiple intravenous infusion to treat gram-negative sepsis. The patients had normal or only moderately reduced renal function as measured by 24-hr creatinine clearances determined on the same day that the kinetic parameters for gentamicin were determined.

Dosage Regimens and Blood Sampling

All patients had been on a fixed regimen of gentamicin therapy for at least 2 days, and were therefore considered to be at steady state. Prior to the study, infusion rates had been adjusted on the basis of observed maximum serum concentrations to provide peak levels in the 5–10 mg/liter range. The drug was infused at a constant rate for 1 hr every 4 hr for periods ranging up to 9 days. The total daily dose of gentamicin in these patients ranged from 5.28 to 16.7 mg/kg (Table II).

Blood samples were drawn prior to the infusion and at 1, 2, and 4 hr after the infusion was begun. Twenty-four hour urines were also obtained for creatinine clearance determinations.

Assay

Serum levels of gentamicin were determined by the method of Lund *et al.* (9). This bioassay employs a stable multiple-antibiotic-resistant strain of *Klebsiella pneumoniae.*

Table II. Patients in the Study and Their Gentamicin Regimens

			Gentamicin therapy		
Patient	Age (yr)	Body weight (kg)	Infusion rate (mg/hr/kg)	Daily dose (mg/kg)	Number of days prior to study
M. B.	1.5	11.2	2.23	13.4	5
M. W.	4	14.4	2.78	16.7	6
C. B.	5	23.2	2.15	12.9	8
D. L.	17	89.1	1.12	6.72	2
B. S.	17	49.5	1.21	7.26	2
J. L.	20	52.3	1.24	7.44	9
W. V. S.	31	64.1	1.40	8.40	4
G. D.	41	69.5	1.37	8.22	4
S. B.	41	84.1	0.89	5.34	4
J. S.	55	46.8	1.50	9.00	6
E. N.	64	68.2	0.88	5.28	3

Computer Fitting of Data

A digital computer program for nonlinear regression analysis (KINA) was used to estimate the individual patient's half-life for gentamicin, and the serum concentrations at the end of the infusion period ($C_{p_{max_\infty}}$) and at the end of the dosing interval ($C_{p_{min_\infty}}$). KINA is an iterative procedure which employs Hartley's modification of the Gauss–Newton gradient method in fitting data to the sum of a series of exponentials (10,11). Serum concentrations determined at 0, 1, and 3 hr during the postinfusion phase were used in fitting the data to a single exponential term (equation 4) using equal weighting of data. The KINA program does not calculate standard deviations for the estimated parameters.

Prediction of $C_{p_{max_\infty}}$ and $C_{p_{min_\infty}}$ in Individual Patients

Maximum and minimum serum concentrations at steady state were calculated for each patient by use of equations 15 and 17 using the computer-generated values for the half-lives. A value of 0.2 liter/kg for the distribution volume and each patient's infusion rate, k_0, were also used in the calculation. The infusion period (t') and infusion interval (τ) were the same for all patients, 1 and 4 hr, respectively.

Calculation of Distribution Volumes

The volumes of distribution of gentamicin in the patients were calculated according to equation 2. The values for k_d, $C_{p_{max_\infty}}$, and $C_{p_{min_\infty}}$ as determined by KINA were used in the calculation.

RESULTS AND DISCUSSION

The half-lives in the patients were found to range between 0.70 and 4.8 hr, with a mean value of 2.1 $\pm$ 1.3 (SD) hr. Other workers have reported the mean half-life in hours ($\pm$SD) for gentamicin to be 3.5 $\pm$ 0.49 in infants (12), 2.5 $\pm$ 1.2 in infants 2–24 months old (13), and 3.2 $\pm$ 1.2 in adults (3).

Seven of the nine patients in whom creatinine clearances were measured during gentamicin therapy had clearances which were quite variable (Table III) but in the normal range (> 80 ml/min/1.73 m^2). Two had creatinine clearances between 60 and 80 ml/min/1.73m^2. The low degree of correlation ($r = 0.31$) between the gentamicin elimination rate constant and creatinine clearance (14) shown in Fig. 4 would not support the use of this index of renal function in establishing gentamicin dosage regimens for these patients. Similar findings have been documented by others (7,15).

The values for the patient's gentamicin half-lives and for $C_{p_{max_\infty}}$ and $C_{p_{min_\infty}}$ as determined by KINA are also given in Table III. The values for

Table III. Patient Parameters and Serum Concentrations of Gentamicin (See Text)

Patient	C_{Cr} (ml/min/ 1.73 m^2)	$t_{1/2}$[a] (hr)	C_{p_0} (mg/liter)	$C_{p_{max}}$[a] (mg/liter)	$C_{p_{min}}$[a] (mg/liter)	$C_{p_{max}}$[b] (mg/liter)	$C_{p_{min}}$[b] (mg/liter)	V_d[c] (liter/kg)
M. B.	106	1.6	3.0	11.6	3.3	11.0	3.0	0.19
M. W.	110	0.70	1.1	9.3	0.48	9.0	0.46	0.19
C. B.	—	1.2	2.1	8.5	1.5	9.1	1.6	0.22
D. L.	139	1.9	1.8	5.0	1.7	6.2	2.1	0.25
B. S.	163	0.71	0.5	4.0	0.21	3.9	0.21	0.20
J. L.	74	1.1	1.4	3.7	0.58	5.0	0.75	0.29
W. V. S.	176	2.1	1.0	8.1	3.0	8.1	3.1	0.20
G. D.	—	3.0	1.9	4.2	2.1	10.2	5.1	0.49
S. B.	64	4.8	7.1	8.7	5.7	9.7	6.4	0.22
J. S.	92	3.9	4.8	11.3	6.7	13.9	7.8	0.25
E. N.	100	2.5	3.7	5.7	2.5	5.7	2.5	0.21

[a]As estimated by KINA.
[b]As estimated by equations 15 and 17 assuming $V_d = 0.20$ liter/kg.
[c]As determined from equation 3, using C_{p_0} and $C_{p_{max}}$ estimated by KINA.

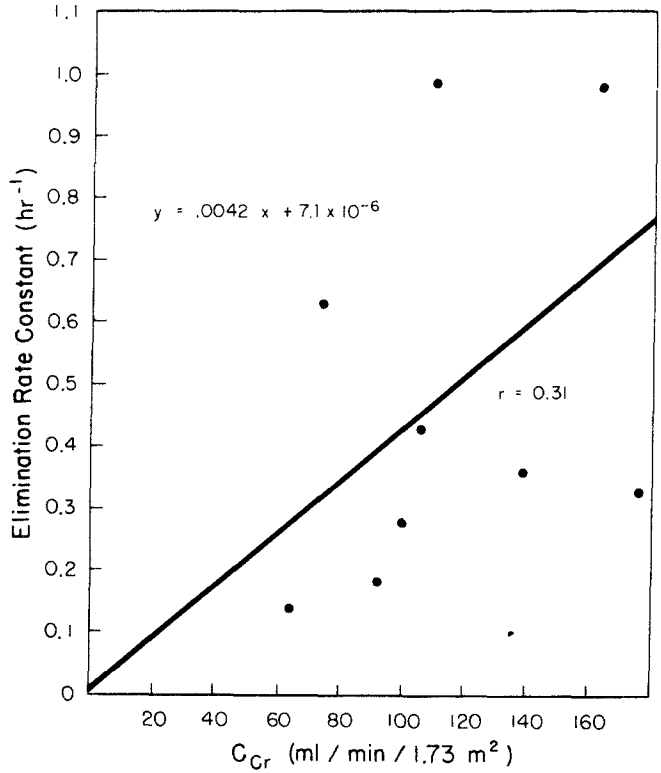

Fig. 4. Relationship between the gentamicin elimination rate constant and creatinine clearance in nine patients with normal or only moderately reduced renal function. The regression line assumes variation in both axes (14).

C_{p_0}, the serum concentrations of gentamicin measured at the start of the infusion, agree reasonably well with the respective values of $C_{p_{\min_\infty}}$, as would be expected under conditions of steady state. Serum concentration–time plots and the computer-fitted curves for four of the patients are shown in Fig. 5.

Assuming a value of 0.20 liter/kg body weight as the volume of distribution for these patients, the calculated steady-state maximum and minimum serum concentrations are compared (Table III) with those estimated by KINA. In each case except one (patient G. D.), there is close agreement. This finding, along with the high degree of variability observed in half-lives, indicates that differences in gentamicin pharmacokinetics in these patients stem mainly from differences in half-life. It is thus expected that a knowledge of a patient's gentamicin half-life may be sufficient to establish a dosing regimen once some steady-state maximum and/or minimum serum concentrations have been chosen.

The distribution volumes calculated by equation 3 are also listed in Table III. That these values are close to the assumed value of 0.2 liter/kg is reflected by the agreement between the $C_{p_{\max_\infty}}$ (and $C_{p_{\min_\infty}}$) values calculated by equation 15 (and equation 17) and those obtained by computer fitting of the data.

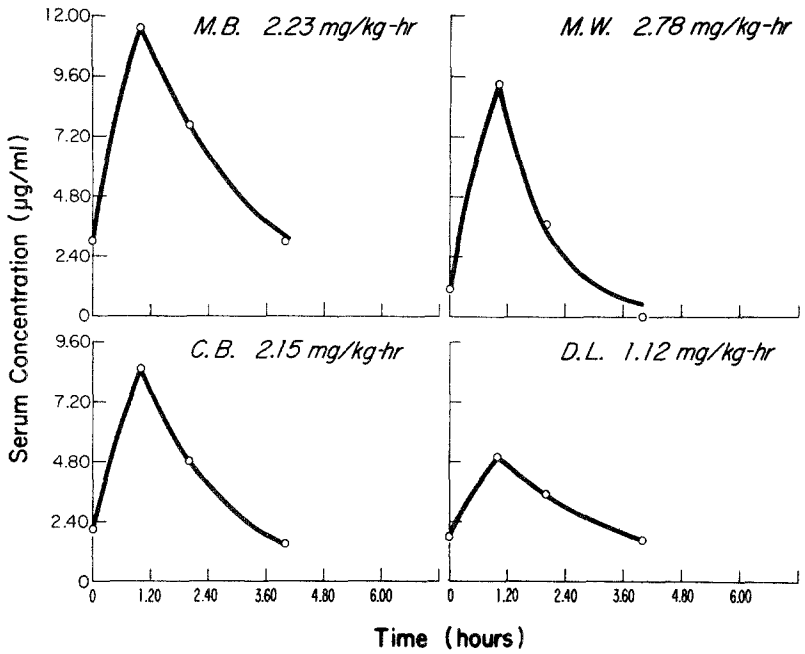

Fig. 5. Plasma concentration–time plots and computer-fitted curves for patients M. B., M. W., C. B., and D. L. Gentamicin was infused for 1 hr (Table II) at 4-hr intervals throughout the course of therapy.

The data in this study were obtained in patients whose regimens had been adjusted to provide adequate serum levels of gentamicin on a trial-and-error basis. Therefore, modification of the patients' regimens using the principles presented here was not attempted. In most patients, more than one adjustment of infusion rates was required to provide peak serum levels in the 5–10 mg/liter range.

Necessary modifications in gentamicin regimens using this approach are presently being evaluated in burn patients in this hospital. This will be the subject of a future report.

In summary, a general approach to the establishment of dosing regimens has been presented for drugs which are given by multiple constant-rate infusions. The method requires a knowledge of the distribution volume and half-life of the drug in the patient. These parameters can be estimated from serum concentration–time data during a multiple intravenous infusion regimen. Where desired maximum and/or minimum steady-state serum concentrations are to be achieved, a convenient infusion period can be chosen, and the appropriate infusion rate and interval can be calculated.

The distribution volumes for gentamicin as determined in this study were relatively constant from patient to patient. Only in one patient (G. D.) did the V_d differ significantly from that of the others. It may be of interest that this patient suffered an electrical burn, while all of the others had received thermal burns. This patient had developed relatively extensive muscle necrosis, requiring the surgical removal of muscle mass prior to the time that his gentamicin parameters were determined.

The measured gentamicin half-lives in these patients ranged from 0.7 to 4.8 hr. This finding suggests that the monitoring of serum gentamicin levels for the purpose of optimizing dosage in these patients may be advisable even in the absence of significantly impaired renal function.

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