Comparison of methods for estimating gentamicin clearance and retrospective analysis of changes in clearance with emphasis on patients with normal renal function

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- 1 The subjects were 29 general medical and surgical patients with apparently normal renal function at the start of treatment with gentamicin.
- 2 Nine methods of estimating gentamicin clearance (CL) were compared as means of calculating gentamicin dosage.
- 3 In 23 of the 29 patients CL was measured twice during treatment. The first measurement was based on 10 blood samples taken around a dose early in treatment. CL calculated from the area under the serum concentration-time curve using all 10 samples was designated a reference method for comparison with other methods.
- 4 There was considerable inter-individual variation in CL. Serum creatinine and body weight gave poor estimates of an individual's CL.
- 5 A good estimate of CL was obtained from four blood samples taken immediately before and 2, 3 and 4 h after dosing.
- 6 Prediction of serum levels is not a good method for checking CL estimations.
- 7 A significant decrease in CL was found during treatment. This was probably due to a reduction in glomerular filtration rate.

Keywords gentamicin clearance renal function

Introduction

Despite their low therapeutic indices the aminoglycosides have been the first choice antibiotics for the treatment of serious gram negative infection for over a decade and are likely to retain this position for some time (Klastersky, 1981; Levin, 1981). Awareness of aminoglycoside toxicity has led to the widespread use of aminoglycoside serum assays and the publication of several

methods for the calculation of aminoglycoside dosage (Davey *et al.*, 1980). Although, it is generally believed that the efficacy of aminoglycoside antibiotics is related to the attainment of an adequate peak level in plasma and that the avoidance of toxicity is best served by a dosage regimen which avoids elevated peaks and troughs (see Davey *et al.*, 1980 for review), the relationship of the mean steady state level (C_{av}) to either efficacy or toxicity has been little studied. A major objective of the present study was the validation of a method for the control of C_{av} . In this context, clearance (CL) is a particularly useful parameter to determine since it is directly related to C_{av} and dosing rate (see equation 1 in **Methods**).

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The main aim of previously published methods for control of gentamicin therapy has been the reduction of dosage for patients with impaired renal function in order to avoid toxicity (Chan *et al.*, 1972; Hewitt, 1974; Hull & Sarubbi, 1976; Mawer *et al.*, 1974; McHenry *et al.*, 1971). Control of dosage in patients with normal renal function has been largely ignored despite the fact that many such patients still receive inadequate doses of the antibiotic (Reymann *et al.*, 1979).

The present study compared different methods for calculating CL of gentamicin, and hence dosage, with particular emphasis on patients with normal renal function. The objectives of the retrospective analysis reported here were (1) to find a clinically practicable method for measurement of CL of gentamicin during a normal 8 h dose interval and (2) to investigate whether CL remained stable in patients with no significant change in serum creatinine (C_{cr}). The results of a study of the outcome of treatment in these patients and an analysis of clinical situations in which adaptive control of gentamicin therapy, based on CL values, may be important are presented elsewhere (Davey *et al.*, 1983).

Methods

Subjects

Twenty nine medical and surgical patients (19 M, 10 F) were studied (Table 1). Their mean age was 51 (range 27 to 76 years) and none was thought to have abnormal renal function at the start of treatment before any measurements were made. Informed consent was obtained from each patient and the study was approved by the Ethics Committee of East Birmingham Hospital.

Gentamicin administration

The decision to treat with gentamicin and the choice of the initial dose were made by the doctor in charge of each patient. The dose of gentamicin was drawn up with a 2 ml insulin syringe using injectable gentamicin, 40 mg ml⁻¹. The dose was injected into the luer of a 20 ml syringe and the first syringe washed out with 2 ml of normal saline which was also injected into the 20 ml syringe. The injection was diluted to a final volume of 20 ml with normal saline and given intravenously (i.v.) over 5 min.

Table 1 Clinical information for the 29 patients at the beginning of treatment. CL was determined by the reference method (10-point AUC).

Patient number	Sex	Age (years)	Body weight (kg)	C_{cr} ($\mu\text{mol/l}$)	$t_{1/2}$ (h)	CL (l h^{-1})
1	M	46	72	84	2.1	5.7
2	M	59	75	115	3.7	6.2
3	M	41	70	87	2.5	4.5
4	F	60	49	44	2.0	10.1
5	M	55	65	81	1.9	6.9
6	F	58	58	76	2.4	4.5
7	M	55	71	82	2.8	4.4
8	F	36	50	72	1.8	5.3
9	F	48	59	67	1.3	6.3
10	M	41	80	79	2.5	6.9
11	F	69	70	86	3.1	4.9
12	M	29	80	88	3.0	4.4
13	M	70	59	87	4.6	3.2
14	M	53	71	81	2.2	6.4
15	M	27	75	98	3.1	3.9
16	M	43	62	75	2.2	9.8
17	F	51	50	64	2.3	3.7
18	M	53	79	114	4.2	4.0
19	M	59	65	95	3.7	5.4
20	F	68	50	78	2.6	4.3
21	F	41	64	79	1.9	7.0
22	M	38	70	440	18.2	1.4
23	F	30	54	95	2.2	3.2
24	M	65	73	117	5.1	2.6
25	F	52	50	490	12.2	0.7
26	M	61	77	176	3.4	3.7
27	M	65	73	80	5.1	2.6
28	M	67	78	137	2.8	2.5
29	M	34	58	89	2.6	12.0

Blood sampling

On each occasion that multiple blood samples were to be withdrawn, a 20 gauge 'butterfly' intravenous cannula was placed in a forearm vein. The cannula was kept patent with a solution of heparin in normal saline, 25 units ml⁻¹. Before each 5 ml blood sample was taken 5 ml of blood were withdrawn and discarded to ensure that no heparin was present in the sample for assay of gentamicin.

Ten blood samples were taken from each patient as early in the course of treatment as possible. Samples were withdrawn immediately before and 15, 30, 45 and 60 min after the dose was given. Five more samples were taken at 30 to 60 min intervals from 2 h after the dose was given. A further set of five blood samples was taken at the end of treatment: these samples were withdrawn before and 0.5, 2, 3 and 4 h after the dose was given. Blood was also taken before and 30 min after an i.v. dose every 3 days during treatment: these are referred to as the trough and peak serum concentrations respectively.

Gentamicin assay

The assay was based on a standard bioassay system (Broughall, 1978). The organism used was *Klebsiella edwardsii* NCTC 10896. A set of five standard gentamicin solutions in serum and four unknown samples were assayed in quadruplicate by distributing them randomly through the test plate. The plate was incubated for 5 h at 42°C or for 16 h at 37°C before the zones of inhibition were read with a Luckham zone reader. The intra-assay coefficient of variation was ≤ 5%.

Creatinine measurements

C_{cr} was measured on each day that samples were taken for gentamicin assay. The routine method was a semi-automated adaptation of the Folín and Wu colorimetric method with picric acid (Technicon Method File N-11B). The range of creatinine concentrations covered was 0 to 1000 $\mu\text{mol l}^{-1}$. In order to obtain more accurate determinations of C_{cr} for correlation with drug elimination rate, C_{cr} was reassayed in the serum samples used to measure CL of gentamicin. The sensitivity of the C_{cr} assay was increased by adjusting the sampling and diluent volumes and by narrowing the range to 0 to 300 $\mu\text{mol l}^{-1}$. The value of C_{cr} was the mean of the concentrations of creatinine in three samples from the early, middle and late portions of the gentamicin elimination curve. Only values of C_{cr} measured in this way were used in the calculation.

Pharmacokinetics

CL, elimination rate constant (k), volume of distribution (V) and C_{av} were calculated by the methods described below. These data were used to calculate the desired dosage for the patient and also to predict serum concentrations at specified times following a subsequent dose. The predictions were based on a one-compartment model (Gibaldi & Perrier, 1975) and were done with the aid of a computer program (Scott, 1981).

The dose to be administered (D , mg) may be calculated from CL using the following relationship

$$D = CL \cdot t \cdot C_{av} \quad (1)$$

where t is the dose interval (h), C_{av} is the desired mean steady-state gentamicin concentration (mg l⁻¹) and the units of CL are l h⁻¹. The value chosen for C_{av} was 2.5 mg l⁻¹. This is the value obtained by taking the recommended dosing schedule of 1.7 mg kg⁻¹, eight-hourly (Kaye *et al.*, 1974) and assuming typical values for k of 0.3 h⁻¹ and for V (1) of 30% body weight in kg.

The area under the serum concentration-time curve (AUC) was determined as for a single dose by the following method (Scott, 1981): k was calculated by linear regression analysis of the logarithms of the serum levels measured 2 h and more after the dose. The area under the curve during the i.v. infusion (AUC₁) was calculated from the formula (Gibaldi & Perrier, 1975)

$$\begin{aligned} \text{AUC}_1 &= \int_0^{t_i} \frac{D}{Vkt_i} (1 - e^{-kt}) dt \\ &= \frac{D}{Vk} \left(1 + \frac{e^{-kt_i}}{kt_i} - \frac{1}{kt_i} \right) \end{aligned} \quad (2)$$

where D = dose administered, V = volume of distribution (assumed to be 30% of actual body weight in this part of the calculation), t_i = duration of infusion (5 min). The concentration at the end of the infusion was calculated by linear back-extrapolation of log concentration values to time $t = t_i$. The effect of the previous doses was eliminated from this concentration and all subsequent measured levels by subtracting from them the values $C^* \cdot e^{-kt}$ (C^* = pre-dose trough level, t = time measured from the beginning of the dose interval). The area under the curve between $t = t_i$ and the last measurement (AUC₂) was calculated by the linear trapezoidal rule (Gibaldi & Perrier, 1975). The area under the curve from the last measurement to time infinity (AUC₃) was calculated from C_L/k where C_L was the concentration calculated at the time of the last measurement from the regression analysis. Thus,

$$AUC = AUC_1 + AUC_2 + AUC_3 \quad (3)$$

Error analysis (Scott, 1981) showed that AUC_1 made only a small contribution to the total AUC, and therefore the assignment of $V = 30\%$ body weight in the calculation of AUC_1 was unimportant. Similarly, the errors in estimating the area from $t = t_i$ to the first post-dose measurement using linear extrapolation for $C(t_i)$ were found to be insignificant, thus eliminating the need to use a two-compartment model to allow for the rapid distribution phase of gentamicin. Although it was necessary to use the calculated value of k to determine AUC, the error thus introduced into AUC_3 was largely cancelled out by an equivalent error in the correction of AUC_2 for the effects of previous doses.

Nine methods for the estimation of CL were compared. The methods differed markedly in the number of blood samples required during a dose interval. Eight methods (Table 2) estimated CL either directly from AUC using relationship (4) or by first estimating the parameters k and V and using relationship (5):

$$CL = \frac{D}{AUC} \quad (4)$$

$$CL = k \cdot V \quad (5)$$

In the ninth method, which is not included in Table 1, an approximation to C_{av} was made by taking the exponent of the mean of the natural

logarithms of the peak and trough concentrations (Barza, 1981). CL may be calculated from this approximate C_{av} using equation (1).

CL calculated from AUC using all ten blood samples taken as early in the treatment as possible was considered to be the reference method. Other methods which used only some of these blood samples were compared to the reference method. CL was calculated from AUC using five blood samples (trough, 0.5, 2, 3 and 4 h) in Method I and using four blood samples (trough, 2, 3 and 4 h) in Method II.

In Methods III to VII CL was calculated as the product of k and V . In those methods in which CL was calculated directly from AUC, k and V were also determined for the purpose of comparison of these parameters with the values obtained in Methods III to VII. In the reference method k was determined by linear regression of the five points in the logarithmic concentration-time plot after 2 h and in Methods I and II by linear regression of three points between 2 and 4 h. V was determined by using equations (4) and (5). Thus

$$V = \frac{D}{k \cdot AUC} \quad (6)$$

Half-life ($t_{1/2}$) was calculated from the reference value of k using

$$t_{1/2} = \frac{0.693}{k} \quad (7)$$

Table 2 Summary of comparisons of methods for calculating k , V and CL in 29 patients. Details of the methods are given in the text. All correlations were significant ($P < 0.02$) except for V by body weight (Methods V to VII, $P > 0.05$).

		Method						
	Reference	I	II	III	IV	V	VI	VII
Estimate of k	5 point regression (after 2 h)	3 point regression (2-4 h)				C_{cr}		
Estimate of V	$\frac{D}{k \cdot AUC}$			adjusted intercept	intercept	30% of body weight		
Estimate of CL	$\frac{D}{AUC}$			$k \cdot V$				
Number of blood samples	10	5	4	4	3	1	1	1
Correlation coefficients with reference method for first dose								
k		0.92	0.92	0.92	0.92	0.71	0.57	0.59
V		0.93	0.92	0.89	0.86	-0.12	-0.12	-0.12
CL		0.99	0.95	0.96	0.87	0.75	0.59	0.58
Mean difference (mg) in dose calculated from cited method and reference method (cited method-reference method)								
		5.2	5.5	-0.68	-15.0	7.66	0.76	7.8
% of calculated doses within 10 mg of reference method								
		62	69	76	33	31	24	24

If AUC is not measured V may be calculated from

$$V = \frac{D}{C_0} \quad (8)$$

where C_0 is a theoretical concentration equal to the serum concentration immediately after complete distribution of a bolus i.v. injection of drug but before any elimination occurs. C_0 may be calculated by extrapolation back to the ordinate of the regression line used to calculate k . The value of C_0 should also be adjusted in multiple dosing to account for the trough level from the previous dose. Method III employed an adjusted C_0 value (C_0 - trough) whilst Method IV used the non-adjusted value. Both methods used k calculated from three blood samples between 2 and 4 h. V may also be estimated from body weight, lean body weight (Hull & Sarubbi, 1974) and body surface area (Siber *et al.*, 1979). For the latter estimates use was made of the lean body weight formulae of Raichlen (1976) and surface area from Documenta Geigy Scientific Tables (1975). It was examined whether the reference value of V correlated with body weight, lean body weight or body surface area. A value of $V = 30\%$ body weight in kg (30% was the average value in the patients in this study) was used for Methods V to VII, together with k estimated from C_{cr} . First, creatinine clearance (CL_{cr} , ml min^{-1}) was estimated from C_{cr} ($\mu\text{mol l}^{-1}$) by the formulae of Jadrony (1965) in Method V, Cockcroft & Gault (1976) in Method VI and Siersbaek-Nielsen *et al.* (1971) in Method VII. Then k was estimated from CL_{cr} by the formula of Michelson *et al.* (1976)

$$k = 0.012 + 0.00324 CL_{cr} \quad (9)$$

Results

Elimination rate constant and half-life

Values of k ranged from 0.038 to 0.533 h^{-1} and $t_{1/2}$ from 1.3 to 18 h. There was a highly significant correlation between $t_{1/2}$ and C_{cr} ($r = 0.92$; slope = 0.031; intercept = 0.145). However, two patients had much higher C_{cr} than the remainder of the group and removal of these two patients gave a weaker but still significant correlation ($r = 0.53$; slope = 0.020; intercept = 1.19). The mean $t_{1/2}$ for 15 patients with C_{cr} values compatible with at least 95% normal renal function for their age and sex (Bjornsson, 1979) was 2.7 h (s.d. = 0.6; range = 1.3 to 3.8 h).

Volume of distribution

The range of V derived from the reference method was 12 to 59% of body weight (mean =

30%; s.d. = 11%). There was no significant correlation between V and body weight, lean body weight or body surface area ($r < 0.2$ in all cases).

Clearance and dose requirements

The range of CL from the first measurements was 0.7 to 12.0 l h^{-1} (mean = 5.1 l h^{-1} ; s.d. = 2.52 l h^{-1}). The mean dose required to give a C_{av} of 2.5 mg l^{-1} was 1.59 $\text{mg kg}^{-1} 8 \text{ h}^{-1}$ (s.d. = 0.93 mg).

Comparison of estimates of parameters

The various methods of estimating k , V and CL were combined to give seven methods of estimating dose and these methods were compared with the reference method (Table 2). A good method should have a high correlation coefficient which shows there is general concordance with the reference method, a small mean error which shows there is little bias towards a high or low estimate and narrow 95% confidence limits which shows precision. In order to relate the analyses to clinical practice the confidence limits are presented (Table 2) as the percentage of calculated doses within 10 mg of the dose calculated by the reference method.

The estimates of V from body weight (Methods V to VII) did not correlate with the reference method and estimates of k from C_{cr} correlated less well with the reference method than estimates of k from three serum drug levels. Consequently, the dosage calculations based on body weight (Methods V–VII) were also poor, yielding only 24 to 31% of doses within 10 mg of the reference method. Method VI, based on the Cockcroft & Gault (1976) calculations, had a very low bias with a mean error of only 0.76 mg, but the spread of the results meant that only 24% were within 10 mg of the correct dose.

The estimate of V from unadjusted C_0 values (Method IV) significantly underestimated CL and hence dose whilst the adjusted C_0 values (Method III) yielded better correlations, a smaller mean error in calculated dose (−0.68 mg compared to −15.0 mg) and narrower confidence limits (76% within 10 mg compared to 33% for Method IV).

Both AUC methods (I and II) tended to overestimate CL and hence dose (mean differences in dose from the reference method were 5.2 and 5.5 mg respectively) but had narrower confidence limits (62% and 69% within 10 mg) and excellent correlations ($r = 0.99$ and 0.95 respectively).

CL calculated from C_{av} estimated from the peak and trough values yielded a mean underdosing of 3.0 mg but only 25% of 24 dose calculations were within 10 mg of the reference method. This method, as well as Method VI,

Table 3 Comparison for seven patients with sudden reduction in renal function of measured C_{av} (using equation 1 and CL determined by Method III) and C_{av} calculated as the mean of the peak and trough levels or from C_{cr} (using equation 1 and CL determined by Method VI). Measured C_{av} is significantly higher than the mean of peak and trough levels ($P < 0.02$) and C_{av} calculated from C_{cr} ($P < 0.01$). Four of the seven patients had clinical evidence of renal impairment. (Reproduced with permission from Davey *et al.*, 1983).

Patient number	Clinical evidence of impaired renal function	Measured C_{av} (mg/l)	C_{av} calculated from peak and trough levels	C_{av} calculated from C_{cr}
10	none	6.9	6.4	3.0
23	hypotension and shock	10.8	7.4	6.8
24	oliguria	11.1	6.1	5.7
25	oliguria	5.8	4.3	2.8
26	hypotension and shock	14.5	10.1	13.3
27	none	4.2	4.4	2.7
28	none	12.1	5.7	3.7

consistently overestimated clearance in patients in whom the measurements were made during unstable, deteriorating renal function (Table 3).

Changes in parameters during treatment

Repeat measurements of CL were made in 23 patients by Method III and compared with the initial measurements of CL by the same method. There was a significant correlation between the percentage change in CL and the percentage change in C_{cr} (Table 4). There was a 50% or greater change in C_{cr} in five patients; changes in CL in the remaining 18 patients did not correlate with changes in C_{cr} (Table 4). CL decreased in 13 of these patients, remained the same in two and increased in three. The changes in CL were reflected by changes in k in nine of the patients with decreased CL and in all of the patients with increased CL. Overall there was a significant tendency towards a reduction in CL (Table 4).

In 16 patients adequate data were available to determine CL on both the first and the second occasion also by Method I (5-point AUC). A significant decrease in CL ($P < 0.01$) was confirmed using this method, and also using the reference method for the first measurement of CL and Method I for the second measurement ($P < 0.01$) (Table 4).

Prediction of serum levels

C_{cr} changed by less than 50% in 22 of the 29 patients. In these patients the parameters measured by the reference method (i.e. using 10 blood samples) were used to predict serum concentrations of the drug in 137 subsequently taken blood samples (Table 5). Although there was a highly significant correlation ($r = 0.81$) between predicted and measured gentamicin levels, the 95% confidence limits were large (56%) and there was a significant tendency to underestimate measured levels. The correlation and underestimation were improved by predicting only samples taken more than an hour after the dose but the 95% confidence limits of the difference between predicted and measured levels remained large (Table 5).

Discussion

In this study the use of CL calculated from AUC (by the method described under *Pharmacokinetics*) in order to estimate dose requirements was stimulated by an awareness of theoretical advantages over the use of k and V :

- (1) it is less dependent upon the model used

Table 4 Changes in CL during gentamicin treatment and correlation with changes in C_{cr}

	$CL_1 - CL_2$ (1 h^{-1}) Mean (s.d.)	$\frac{CL_1 - CL_2}{CL_1} \%$ Mean (s.d.)	Correlation between % changes in CL and C_{cr}
23 patients	1.36 (1.55), $P < 0.01$	18.5 (29)	0.743, $P < 0.001$
18 patients with < 50% change in C_{cr}	1.04 (1.43), $P < 0.001$	11.4 (13)	0.373, $P > 0.1$

Table 5 Predictions of serum levels of gentamicin in 22 patients with < 50% change in C_{cr} during treatment. Parameters estimated using all 10 blood samples were used in the calculations.

	Correlation between predicted and measured serum levels	Mean error predicted – measured predicted %	95% confidence limits
137 samples	$r = 0.81$	-17.1	56%
100 samples taken more than 1 h after a dose	$r = 0.85$	-13.5	47%

- (2) no assumptions are made about being at steady-state
- (3) the result is independent of the previous doses.

However the results of the study suggest that the advantages of determination of CL from AUC instead of directly from k and V may be negated if AUC is not determined by an accurate method involving collection of at least five blood samples during a dose interval.

CL values showed large inter-individual variation. CL calculated from C_{cr} and body weight was not significantly different from the reference values because the difference between the methods had large standard deviations indicating a large random difference between the methods. All of the methods based on C_{cr} and body weight were poor for calculating gentamicin dose because there was no correlation between V and body weight. Re-assay for C_{cr} by an accurate method excluded the possibility of a significant contribution from analytical error of C_{cr} in our study. Lean body weight (Hull & Sarubbi, 1976) and surface area (Siber *et al.*, 1979) are said to be better guides to dosage than actual body weight but this has not been confirmed by Evans *et al.* (1979) or by the present study. Of the methods based on body weight, Method V (Table 2) gave marginally better results because the Jadrony formula (1965) gave the best estimate of k from C_{cr} . Overall Method III was best with 76% of the 29 doses within 10 mg of the reference method. The alternative method for calculating CL from four blood samples (Method II) overestimated CL although for practical purposes, i.e. dose calculation, the results were similar to Method III (Table 2). Addition of a 30 min sample did not improve the results (Method I). The mean logarithmic serum concentration was a relatively poor method for calculating dose in comparison to Methods I and III. This was expected because C_{av} will always be underestimated by this method (Gonda, 1982).

The changes in CL observed in patients with apparently stable renal function may be due to any of the following:

- (1) laboratory error
- (2) use of a one- rather than a two-compartment model
- (3) changes in glomerular filtration rate (GFR)

Laboratory error was small and would not contribute to a marked trend such as is exhibited by these data. Simulations were performed using standard NAG algorithms on a CDC 7600 computer to estimate the expected errors in the measured parameters, k , V and CL that would result from analytical error at several levels. At the level of analytical error in this study ($\leq 5\%$) the maximum error in CL from this source alone should be 7.5% (mean error = 1.6%) whereas errors in k and V could be as high as 21%.

The changes in CL calculated by Method III were confirmed in the majority of patients by Method I. This method, based on AUC, yields CL which is almost independent, in the mathematical sense, of k (see under 'Pharmacokinetics' in **Methods** section). Thus, if the calculation of CL is largely independent of the one compartment rate constant, k , it is highly unlikely that observed changes in CL could be attributed to the use of an inappropriate pharmacokinetic model.

Changes in CL did not correlate significantly with changes in C_{cr} of less than 50%. This does not exclude changes in GFR as a cause of changes in CL because Trollfors (1980) showed a mean 10% reduction in GFR, as measured by ^{51}Cr EDTA clearance, in 36 gentamicin-treated patients with no significant changes in C_{cr} . No such reduction in GFR occurred in a similar group of patients treated with cefuroxime. There is recent evidence that gentamicin causes changes in glomerular ultrafiltration coefficient which parallel changes in whole kidney GFR (Bayliss *et al.*, 1980) and may be related to changes in filtration area in the glomerular endothelial cells (Avasthi *et al.*, 1981). Since gentamicin is eliminated from the body almost entirely by the kidney it is probable that a reduction in GFR was mainly responsible for the overall significant reduction in CL in our study (Table 3).

Prediction of subsequent serum levels had

been used as a guide to the accuracy of initial estimates of pharmacokinetic parameters (Chow *et al.*, 1978; Michelson *et al.*, 1976). In the present study there was a highly significant correlation between predicted and measured levels although the 95% confidence limits were large (56%) and the predictions significantly underestimated the measured levels. Predictions made by computer simulations of patients with no real change in parameters, but with appropriate analytical errors, showed no significant difference between the 'predicted' and 'measured' levels, but showed 95% confidence limits of approximately 30% (Scott, 1981). Thus the precision of the clinical predictions was less than that expected from simulations and there was a serious bias in the results towards underprediction. This underprediction would be expected from the finding of an overall decrease in gentamicin CL during treatment. The underprediction was reduced by excluding samples taken within an hour of the dose because a one-compartment model does not allow for the higher concentrations which occur during the distribution phase after an i.v. injection. This improvement did not greatly influence the 95% confidence limits of the difference between predicted and measured levels. Clearly, if CL of gentamicin changes during treatment then prediction of subsequent

serum levels cannot be used as a guide to the accuracy of initial estimates of pharmacokinetic parameters.

It is also apparent that differences between predicted and measured serum levels can be only a very rough guide to changes in CL for two reasons. The first is a consequence of the limitations imposed by the use of a one-compartment model; it neglects the effect of a second 'deep' compartment which would be to increase the serum level slightly with time. Secondly, apparent errors in prediction might be explained in part by inaccurate timing of doses between the measurement of CL and the subsequent serum level. A delay of 1 h in the timing of penultimate dose could cause an increase of 25% in the level 4 h after the final measured dose. Measurements of CL (with a trough level) are not affected by errors in timing of previous doses. If CL measurements are to be used as a guide to gentamicin dosage then they must be repeated regularly during treatment instead of, or in addition to, measurement of C_{cr} or peaks and troughs.

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References

- Avasthi, P. S., Evan, A. P., Huser, J. W. & Luft, F. C. (1981). Effect of gentamicin on glomerular ultrastructure. *J. lab. clin. Med.*, **98**, 444-454.
- Barza, M. (1981). Principles of tissue penetration of antibiotics. *J. antimicrobial Chemother.*, **8** Suppl. C, 7-28.
- Bayliss, C. (1980). The mechanism of the decline in glomerular filtration rate in gentamicin-induced acute renal failure in the rat. *J. antimicrobial Chemother.*, **6**, 381-388.
- Bjornsson, T. D. (1979). Use of serum creatinine concentration to determine renal function. *Clin. Pharmacokin.*, **4**, 200-222.
- Broughall, J. M. (1978). Aminoglycosides. In *Laboratory methods in antimicrobial chemotherapy*, eds. Reeves, D. S., Phillips, I., Williams, J. D. & Wise, R., pp 194-207. Edinburgh: Churchill Livingstone.
- Chan, R. A., Benner, E. J. & Hoeprich, P. D. (1972). Gentamicin therapy in renal failure: nomogram for dosage. *Ann. Int. Med.*, **76**, 773-778.
- Chow, M., Deylin, J., Harralson, A., Artlett, R. & Quintiliani, R. (1978). Prediction of gentamicin serum levels using a one compartment open linear pharmacokinetic model. *Am. J. hosp. Pharm.*, **35**, 1078-1081.
- Cockcroft, D. W. & Gault, M. H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**, 31-41.
- Davey, P. G., Geddes, A. M., Gonda, I., Harpur, E. S. & Scott, D. K. (1983). Clinical experience with a method of adjusting gentamicin dose using measured drug clearance. *J. antimicrobial Chemother.*, (in press).
- Davey, P. G., Gonda, I., Harpur, E. S. & Scott, D. K. (1980). Review of recent studies on control of aminoglycoside antibiotic therapy. *J. clin. hosp. Pharm.*, **5**, 175-195.
- Evans, W. E., Felman, S., Ossi, M., Taylor, R. H., Chaudhary, S., Melton, E. T. & Barber, L. F. (1979). Gentamicin dosage in children: A randomised prospective comparison of body weight and body surface area as dose determinants. *J. Pediatrics*, **94**, 139-143.
- Gibaldi, M. & Perrier, D. (1975). *Drugs and the pharmaceutical sciences*, Vol. 1. Pharmacokinetics. New York: M. Dekker Inc.
- Gonda, I. (1982). On prediction of free antibiotic (cefazoline) concentrations in extravascular fluids from 'logarithmic mean serum concentrations'. *J. antimicrobial Chemother.*, **9**, 53-56.
- Hewitt, W. L. (1974). Gentamicin toxicity in perspective. *Postgrad. med. J.*, **50** Suppl. 7, 55-59.
- Hull, J. H. & Sarubbi, E. A. (1976). Gentamicin serum concentration: Pharmacokinetic predictions. *Ann. int. Med.*, **65**, 183-189.
- Jadry, L. (1965). Odhad Glomerularni Filtrace-Z-

- Kreatininemie. *Casopis Lekarů Ceských*, **104**, 947–949.
- Kaye, D., Levison, M. E. & Labovitz, E. D. (1974). The unpredictability of serum concentrations of gentamicin: pharmacokinetics of gentamicin in patients with normal and abnormal renal function. *J. infectious Dis.*, **130**, 150–154.
- Klastersky, J. (1981). Clinical efficacy of aminoglycosides: an example of balance between microbiology and pharmacology. *J. antimicrobial Chemother.*, **8**, Suppl. A—1143–149.
- Levin, S. (1981). Antibiotics of choice in suspected serious sepsis. *J. antimicrobial Chemother.*, **8**, Suppl. A: 133–142.
- Mawer, G. E., Ahmed, R., Dobbs, S. M., McGough, J. C., Lucas, S. B. & Tooth, J. A. (1974). Prescribing aids for gentamicin. *Br. J. clin. Pharmacol.*, **1**, 45–50.
- McHenry, M. C., Gavan, T. L., Gifford, R. W., Gewkink, N. A., Van Ommen, R. A., Town, M. A. & Wagner, J. G. (1971). Gentamicin dosages for renal insufficiency. *Ann. int. Med.*, **74**, 192–197.
- Michelson, P. A., Miller, W. A., Warner, I. F., Ayers, L. W. & Boxenbaum, H. G. (1976). Multiple dose pharmacokinetics of gentamicin in man: Evaluation of the Jelliffe nomogram and the adjustment of dosage in patients with renal impairment. In *The effect of disease states on pharmacokinetics*, ed. Benet, L. Z., pp 207–245. Washington: American Association and Academy of Pharmaceutical Sciences.
- Raichlen, J. S. (1976). Calculating gentamicin doses. *Ann. int. Med.*, **85**, 827–828.
- Reymann, M. T., Bradac, J. A., Cobbs, C. G. & Dismukes, W. E. (1979). Correlation of aminoglycoside dosages with serum concentrations during therapy of serious gram-negative bacillary disease. *Antimicrobial Agents Chemother.*, **16**, 353–361.
- Scott, D. K. (1981). *High-performance liquid chromatography and pharmacokinetics of some antibiotics*. Ph.D. Thesis, University of Aston in Birmingham.
- Siber, G. R., Smith, A. L. & Levin, M. J. (1979). Predictability of peak serum gentamicin concentration with dosage based on body surface area. *J. Paediatrics*, **94**, 135–138.
- Siersbaek-Nielsen, K., Hanssen, J. M., Kampmann, J. & Kristensen, M. (1971). Rapid evaluation of creatinine clearance. *Lancet*, **i**, 1133–1134.
- Trollfors, B. (1980). Quantitative studies on antibiotic nephrotoxicity. *Scand. J. infect. Dis., Suppl.* **21**, 21.

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