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Accumulation Pharmacokinetics of Tobramycin

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Tobramycin pharmacokinetics is usually described by a one-compartment model, but this model fails to account for both the incomplete urinary recovery and prolonged post-treatment persistence noted with this drug. We examined the multiple-dose behavior of tobramycin in 35 treated patients with stable renal function, using peak and trough serum concentrations, urine recovery, and postmortem tissue analysis. Serum concentrations rose slowly throughout treatment and declined in two phases after the drug was stopped. The first-phase half-life correlated well with renal function, but the second averaged 146 h and was poorly related to creatinine clearance. A two-compartment model was used to describe the biphasic decline in serum concentrations and to calculate the amount of drug in the tissue compartment at all times during and after treatment. Predicted tissue amounts rose continually throughout treatment in all study patients. In 5 patients, the total amount of tobramycin in the body after the final dose was recovered in the urine, but urine had to be collected for 10 to 20 days to achieve complete recovery of the drug. In four patients, the predicted tissue amount was recovered from postmortem tissues. Regardless of the dose, tobramycin accumulated in the tissues of all patients receiving this antibiotic. The two-compartment pharmacokinetic model explains both the rising peak and trough concentrations during treatment and the detection of the drug in serum and urine long after the last dose.

Tobramycin is an aminoglycoside antibiotic effective against most aerobic gram-negative bacilli. This drug has been in clinical use since 1975, and it is usually considered an alternate to gentamicin.

The pharmacokinetics of tobramycin has been studied in both normal volunteers (9, 10) and patients (3), and are generally thought to be similar to those of gentamicin. The drug has a half-life of about 2 h when renal function is normal, and this half-life varies inversely with decreases in creatinine clearance (C_{Cr}) (1). Although tobramycin is not metabolized, previous investigators have not recovered the total administered dose in the urine of normal volunteers (9, 15). In spite of this observation, the pharmacokinetics of tobramycin is usually described by a one-compartment pharmacokinetic model.

Recent observations with gentamicin suggest that the one-compartment model does not provide an adequate description of the pharmacokinetics of this aminoglycoside. Gentamicin persists for prolonged periods in all body tissue and is easily detected in serum and urine for weeks after the final dose (4). We have recently explained these findings with a two-compartment pharmacokinetic model and found that gentamicin has a terminal half-life of over 100 h in all patients, which is due to tissue persistence (12). Since tobramycin also persists in serum, urine, and tissues for prolonged periods (J. J. Schentag, J. W. Vance, L. M. Gerbracht, T. J. Cumbo, and W. J. Jusko, Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 16th, Chicago, Ill., Abstr. 385, 1976), we sought to characterize the pharmacokinetics of tobramycin by using a two-compartment model.

MATERIALS AND METHODS

We studied 35 hospitalized patients who required tobramycin for treatment of severe infection. The patients ranged in age from 22 to 87 years, with a mean of 63 years. Seventy-one percent of these were seriously ill and managed in acute-care units. All patients had serious underlying heart or lung disease, diabetes, or complex postoperative problems. The site of infection varied: 17 patients had pneumonia, 8 had pyelonephritis, 2 had bacterial endocarditis, and the remainder had abdominal or unidentified infections. Six (17%) had positive blood cultures, but none had septic shock when studied.

The 35 patients had stable renal function through-

out the course of treatment, as assessed by serial determination of serum creatinine. C_{Cr} was estimated from serum creatinine (13) in all patients and from 24-h urine collection in 20. The measured and estimated values were usually in good agreement, with major discrepancies generally traced to incomplete collection of urine specimens. C_{Cr} in the population averaged 72 ml/min and ranged from 22 to 150 ml/min.

Sampling. Venous blood samples were obtained at peak (1 h after intramuscular or immediately after a 1-h intravenous infusion), midpoint, and trough (just before dose) times throughout the treatment course at usual intervals of 2 to 4 days. Serum concentrations were also obtained at 24-h intervals for 5 to 20 days after the final dose of tobramycin for characterization of the terminal half-life of the drug. Tissue samples were obtained postmortem (usually kidney, liver, lung, heart, skeletal muscle, fat, bone, spleen, pancreas, and brain) in patients who expired during treatment or in the 30 to 60 days after the final dose.

Assays. Serum concentrations were determined by both microbiological (14) and radioimmunoassay (RIA) methods, in similar fashion and with similar reproducibility to our previously reported gentamicin studies (12). In the microbiological assay, penicillinase was incorporated into the agar, and samples containing cephalosporins were diluted with β-lactamase enzyme. Samples containing other interfering antibiotics were assayed by RIA only. RIA was also used exclusively to determine the very low washout concentrations (<0.25 μg/ml). Tissue concentrations were determined by the prolonged elution method we have previously described for gentamicin (11; Schentag et al., 16th ICAAC). The tissue concentrations were multipled by the organ weight to determine the amount of tobramycin in the organ.

Pharmacokinetic analysis. The decline in serum concentrations after the final dose was fitted to a two-compartment model by using the computer program NONLIN as previously described (11; Schentag et al., 16th ICAAC). The pharmacokinetic parameters for distribution and elimination derived from the computer fit of the washout serum concentrations were used to simulate both serum concentrations and tissue amounts for each study patient. The accuracy of these simulations was tested by measuring tissue and serum concentrations of tobramycin as well as amounts appearing in the urine.

RESULTS

Population characteristics. Table 1 provides a summary of the clinical characteristics of these 35 patients, with the population divided into three groups based on renal function. Patients with lower C_{Cr} values were slightly older and thinner. No significant differences were noted in the duration of treatment, exposure to cephalosporins and diuretics, hematocrit, or serum concentrations of tobramycin among the groups. Greater total doses were given to patients with higher C_{Cr} values. However, the resulting serum concentrations were similar in all three groups, reflecting that pharmacokinetic

TABLE 1. *Clinical comparison of 35 patients receiving tobramycin*[a]

C_{Cr} group	Parameter						Concurrent drugs		Serum concn (μg/ml)				
	No.	Age (yr)	Wt (kg)	C_{Cr} (ml/min)	Total dose (g)	Duration (days)	Cephalosporins	Diuretics	1st peak	Final peak	1st trough	Final trough	Hematocrit (%)
0–50	10	71 ± 10	65 ± 16	31 ± 9	1.0 ± 0.6	10 ± 3	3 (30)[b]	2 (20)[b]	5.2 ± 1.2	5.9 ± 1.8	1.3 ± 0.7	1.7 ± 0.9	31 ± 5
51–75	9	68 ± 8	69 ± 13	63 ± 8	2.0 ± 2.1	11 ± 12	3 (33)	3 (33)	5.8 ± 2.3	6.5 ± 1.9	1.4 ± 0.6	1.6 ± 0.8	33 ± 6
76–150	16	55 ± 12	73 ± 8	103 ± 25	2.7 ± 2.7	12 ± 11	5 (31)	3 (19)	5.0 ± 1.6	5.8 ± 1.6	0.7 ± 0.4	1.1 ± 0.8	30 ± 13
Composite (0–150)	35	63 ± 13	70 ± 12	72 ± 36	2.1 ± 2.2	11 ± 10	11 (31)	8 (23)	5.3 ± 1.7	6.0 ± 1.7	1.0 ± 0.6	1.4 ± 0.9	33 ± 6

[a] Values represent mean ± 1 standard deviation.
[b] Numbers in parentheses are percentages.

data generated in this study were obtained in patients given doses adjusted for decreasing renal function. Examining the composite data, there was a significant increase in both peak ($P < 0.01$) and trough ($P < 0.05$) serum concentrations over the duration of treatment, without significant changes in renal function. The tendency for increases in both peak and troughs was also seen in all patient groups, but was not statistically significant in all of the groups due to smaller numbers of patients studied. Pharmacokinetic description of these rising peak and trough serum concentratons required either a constantly declining one-compartment elimination constant or the assumption that the rising concentrations reflect a previously undetected longer terminal half-life.

After the final dose of tobramycin, the serum concentrations fell in two phases, with the first phase equal to the decline in serum concentrations after each maintenance dose. The second phase had a mean half-life of 146 h and was detected beginning about 24 h after the final dose in patients with normal C_{Cr}. Tobramycin disposition was variable in the study patients. To illustrate the typical variability, washout serum concentrations from seven patients with widely varying C_{Cr} values are shown in Fig. 1. First-phase half-lives generally were prolonged as C_{Cr} declined, but the half-life of the second phase was not predictable from renal function and was often longer in patients with normal renal function than in patients with severe renal impairment. A two-compartment linear model was used to describe the biphasic decline in serum concentrations for each patient, and the slope and intercept values were used to predict the distribution and elimination of tobramycin. This model successfully described each patient, in spite of the differences noted between individual patients.

Table 2 shows the calculated pharmacokinetic parameters that describe tobramycin distribution and elimination. Provided are the distribution volumes, both central (V_c) and steady state (Vd_{ss}). The distribution and elimination parameters (α, β, k_{12}, k_{21}, k_{el}, Cl_B, $t_{1/2\beta}$) are also summarized.

Also shown in Table 2 is the predicted amount of tobramycin in the tissue compartment after the final dose (X_T) and assuming dosing was continued to steady state (X_{Tss}). As would be expected with a terminal half-life over 140 h, few patients were treated long enough to achieve steady state. The entire population averaged only 58% of steady state in an average treatment course of 10 days (Table 2).

Tobramycin distribution. Tobramycin volumes of distribution are shown in relation to C_{Cr} in Fig. 2. As found in most previous studies, the volume of the central compartment was similar to extracellular water volume (9, 10). Although the overall observation was that of great intrapatient variation, there was a tendency for the central compartment volume to decrease and for steady-state volumes to increase in patients with higher C_{Cr} values. Neither of these trends was statistically significant, indicating that there was little relationship between renal function and tobramycin volume of distribution. No significant relationships could be identified between the volume of the central or total body compartments and the hematocrit when these relationships were treated by using linear regression analysis.

When factors other than renal function were examined by linear regression analysis, we could not find statistically significant relationships between age and V_c or ideal body weight and V_c. However, our population was of similar age and few patients were markedly obese; therefore these relationships remain of interest in future

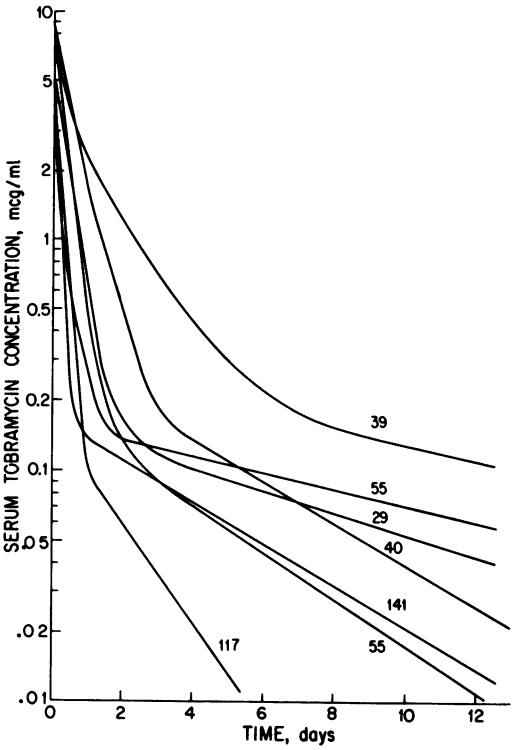

FIG. 1. *Serum concentration versus time curves for seven patients after the last dose of tobramycin. For each patient, C_{Cr} is shown on the slope of the second phase of the washout.*

TABLE 2. *Pharmacokinetic comparison of 35 patients receiving tobramycin*[a]

C_{Cr} group	Parameter											
	No.	$\alpha(h^{-1})$	$\beta(h^{-1})$	$k_{12}(h^{-1})$	$k_{21}(h^{-1})$	$k_{el}(h^{-1})$	V_c(l/kg)	Vd_{ss}(l/kg)	Cl_B (ml/min)	$t_{1/2\beta}$(h)	X_T(mg)	X_{Tss}(mg)	% of steady state achieved
0–50	10	0.083±0.02	0.005±0.002	0.01±0.007	0.006±0.003	0.07±0.03	0.25±0.07	0.74±0.27	18±7	166±64	64±29	105±66	56±22
51–75	9	0.17±0.06	0.007±0.005	0.02±0.01	0.008±0.006	0.16±0.05	0.27±0.12	1.2±1.2	44±16	157±114	110±89	190±132	58±23
76–150	16	0.25±0.06	0.007±0.004	0.03±0.01	0.008±0.005	0.22±0.06	0.26±0.09	1.1±0.6	67±26	129±54	105±45	200±122	62±20
Composite (0–150)	35	0.18±0.09	0.006±0.004	0.02±0.01	0.007±0.005	0.16±0.08	0.26±0.09	1.1±0.9	47±29	146±75	95±58	171±116	58±22

[a] All values represent mean ± 1 standard deviation.

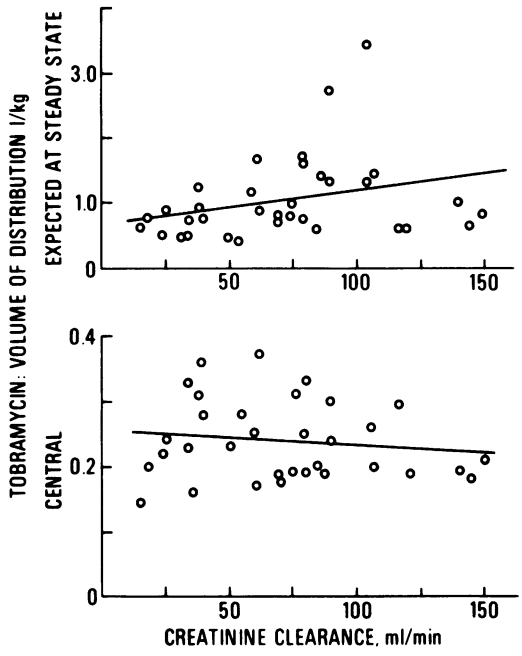

FIG. 2. *Tobramycin distribution volumes versus C_{Cr}. The regression line for central volume versus C_{Cr} is described by the equation $V_c = 0.26–0.00023\ (C_{Cr})$, $r = 0.16$, P = not significant. For the steady-state volume, $Vd_{ss} = 0.0046\ (C_{Cr}) + 0.69$, $r = 0.26$ P = not significant.*

studies. There was no apparent relationship between sex and V_c or Vd_{ss} in the population.

The transfer rate constant k_{12} (transfer into the tissue compartment) and k_{21} (exit from the tissue compartment) varied considerably among the 35 patients. These rate constants are shown in relation to C_{Cr} in Fig. 3. The data demonstrate the large variability in the relationship with a slight, but insignificant, tendency for both constants to be increased in patients with higher C_{Cr} values. Each of the three patient groups had a mean k_{12} value greater than k_{21} (Table 2); therefore, the net amount of drug in the tissue compartment would be expected to increase with each dose administered, since on average the drug entered the compartment faster than it was removed. Accumulation in the tissue compartment would continue until either a steady state is achieved (when input = output) or the drug is discontinued and tissue release is the dominant factor.

Tobramycin elimination. Tobramycin is eliminated from the body solely or almost entirely by the kidney. Previous investigators, using a one-compartment model, used a single overall elimination constant (k = 0.693/rapid $t_{1/2}$) to describe tobramycin elimination from the

body (1). The correlation between k and C_{Cr} was usually linear, but considerable scatter was generally observed in the relationship. Our data for k versus C_{Cr} (Fig. 4) exhibit a linear but variable relationship between the k determined from the first slope of the washout and the C_{Cr} ($r = 0.76$, $P < 0.01$). If renal excretion is the only factor influencing the decline in serum concentrations, this correlation coefficient should be better. The slope of the second phase (β) (Fig. 4) yielded an average β half-life of 146 h (range, 33 to 428 h), but this value was extremely variable between the study patients and was not statistically related to C_{Cr} ($r = 0.25$, P = not significant).

Because neither of the individual disposition rate parameters (k, β) is strongly predictable by considering the influence of renal excretion alone, we also calculated the body clearance (Cl_B) for each patient. Calculating the Cl_B for tobramycin did not improve predictability of the disposition of this drug in relation to renal function ($r = 0.66$, $P < 0.01$) (Fig. 5). The Cl_B of tobramycin averaged 66% of the C_{Cr}, which reflects glomerular filtration and partial tubular reabsorption of the drug. These data demonstrate that tobramycin disposition is apparently influenced by many factors in addition to C_{Cr}.

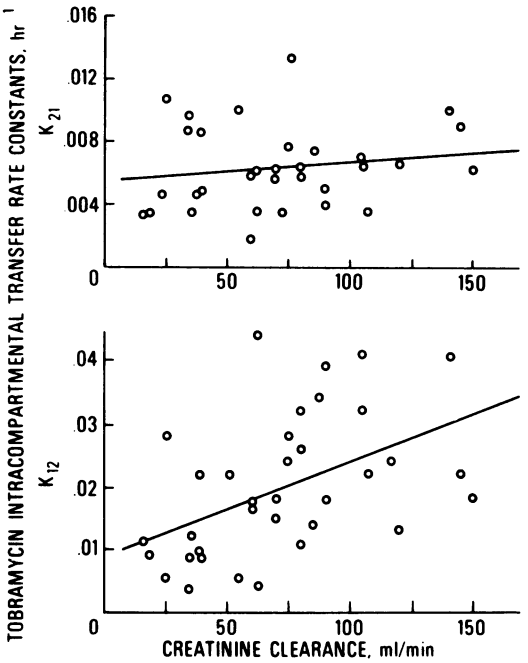

FIG. 3. *Tobramycin intracompartmental transfer rate constants versus C_{Cr}. The k_{12} (rate into the tissue compartment) versus C_{Cr} is described by the regression line $k_{12} = 0.00015\ (C_{Cr}) + 0.0091$, $r = 0.47$, $P < 0.01$. The regression line for k_{21} (rate of exit from the tissue compartment) versus C_{Cr} is described by the equation $k_{21} = 0.000011\ (C_{Cr}) + 0.0055$, $r = 0.16$ P = not significant.*

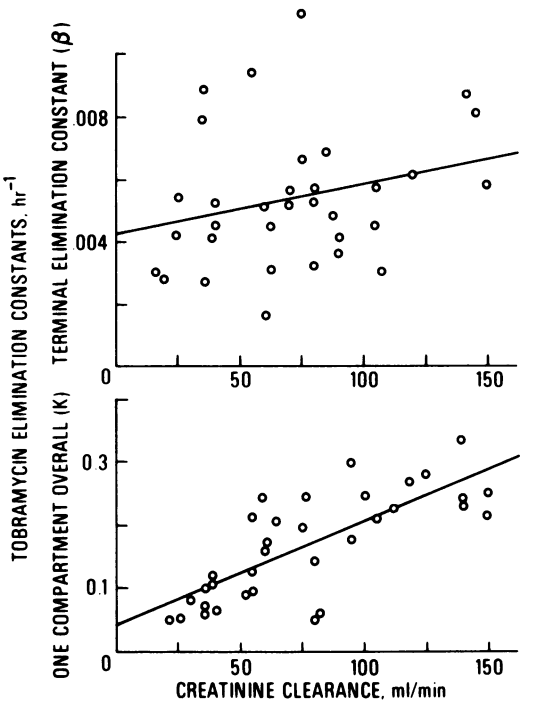

FIG. 4. *Tobramycin elimination constants versus C_{Cr}. The relation between k (one compartment) and C_{Cr} is described by the regression equation $k = 0.0016(C_{Cr}) + 0.04$, $r = 0.76$, $P < 0.01$. The relationship between CCr/70 kg and k was described by the equation $k = 0.0017(C_{Cr}) + 0.04$, $r = 0.71$, $P < 0.01$, indicating that adjustment of body weight did not improve the relationship. The relation between β (terminal) and C_{Cr} is described by the regression equation $\beta = 0.000015(C_{Cr}) + 0.0042$, $r = 0.25$, P = not significant.*

Tissue kinetics. Serum concentrations throughout the course of therapy and from the washout phase were used to calculate the amount of tobramycin present in the tissue compartment of the two-compartment model. For the 35 patients, the average amount of tobramycin present in the tissue compartment immediately after administration of the final dose was 95 ± 58 mg. In Fig. 6, the calculated amount of drug in the tissue compartment is provided for each patient in relation to C_{Cr}. It is noteworthy that in these patients, who received tobramycin at a dosing rate normalized for renal function, there was no significant correlation between renal function and the amount of drug predicted to be in the tissue compartment. This was true either after the final dose or at eventual steady state if dosing was continued to that point. The patient population data are grouped

according to C_{Cr} in Table 2. Renal function appeared to have little influence on the amount of tobramycin in tissues, since each of the three groups accumulated about the same amount of drug in tissues. These data establish that provided dosing rate is decreased with declining C_{Cr}, no greater degree of tissue accumulation will result in patients with impaired renal function.

Tissue recovery. Four patients expired during or after treatment, and their tissues were analyzed for tobramycin. The total recovery of tobramycin from body tissues is compared with the computer-predicted accumulation in Table 3. Considerable intrapatient variability in accumulation of the drug was observed, but the autopsy findings of all patients agreed well with the predictions of the model. This finding confirms the two-compartment model for tobramycin disposition. The mathematical relationships describing tobramycin distribution, described in the table legend, are based on an observed sharp distribution gradient of tobramycin between intravascular and extravascular spaces.

In three of four patients (no. 2, 3, and 5), the postmortem serum concentration was exceeded by the measured concentration in each tissue. Serum concentrations in these three patients were less than 0.2 μg/ml. The highest tissue concentrations were found in the kidney cortex, all of which were above 20 μg/g. In the other patient (no. 9), the postmortem serum concentration was 5.0 μg/g, which was exceeded only by the concentration in the kidney. These results are explained by the rapid washout of the drug from serum and other body fluids and by prolonged persistence of tobramycin in all body tissues.

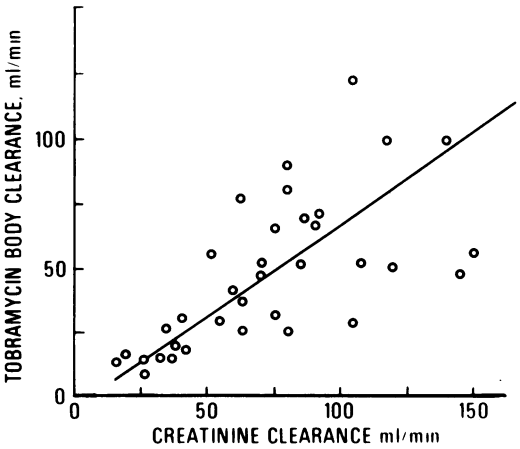

FIG. 5. *Relation between tobramycin body clearance (Cl_B) and C_{Cr} is described by the regression equation $Cl_B = 0.71(C_{Cr}) - 4.1$, $r = 0.65$, $P < 0.01$. If the regression line is forced through the origin, the regression equation describing this relationship is $Cl_B = 0.66(C_{Cr})$, $r = 0.66$, $P < 0.01$.*

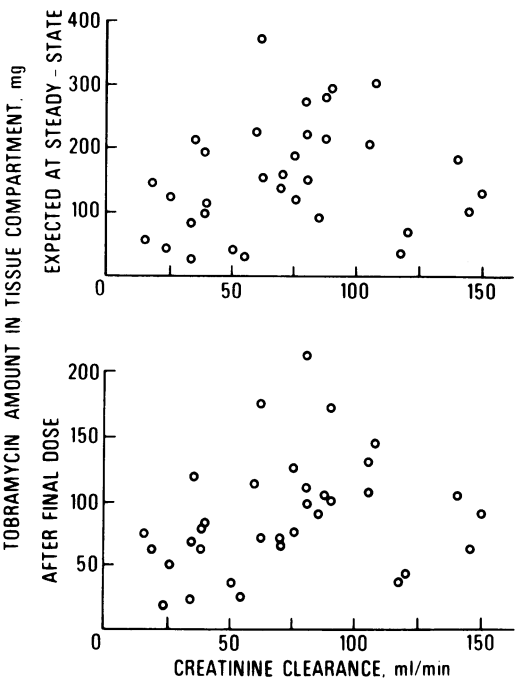

FIG. 6. *Tobramycin accumulation in the tissue compartment for 35 patients. There was no relationship between C_{Cr} and the amount in tissues, either after the final dose or at steady state had dosing continued. After the final dose, 95 ± 58 mg was present, and at steady state, 172 ± 116 mg would have been in the tissue compartment for these patients.*

To test the reliability of the two-compartment model predictions in patients who survived, we collected total urine to quantitate excretion rate and recovery. The results for five patients (no. 1, 4, 6, 7, and 8) are shown in Table 3. Essentially, complete recovery of the predicted amount in tissues required at least 10 days of urine collection after the final dose. Since the total dose was recoverable in urine, tobramycin was probably not metabolized, and previous investigators noted incomplete urine recovery because urine was not collected long enough after the last dose.

DISCUSSION

Rising peak and trough serum antibiotic concentrations on multiple dosing have not been previously noted for tobramycin, but have been observed repeatedly with gentamicin (2, 8). Since no change in C_{Cr} occurred in the study patients, we explain the rising peak and trough concentrations noted in these patients on the basis of slow tissue uptake and release and on the basis of a previously undetected longer ter-

TABLE 3. *Predicted versus measured urine and tissue recovery of tobramycin*

Patient no.	Time period (h)	Amt predicted (mg)	Amt measured[a] (mg)	Confirmed amt by:	Percent agreement between predicted and measured
1	0–240	79.0	81.0	Urine	97.5
2	99.0	32.8	34.2	Tissue	95.9
3	51.0	130.0	152.0	Tissue	85.5
4	0–350	167.0	198.0	Urine	84.3
5	242.0	74.7	61.0	Tissue	122.4
6	0–240	165.1	170.2	Urine	97.0
7	0–240	71.0	72.6	Urine	97.8
8	0–414	192.5	212.0	Urine	90.8
9	1.25	51.1	57.2	Tissue	89.3

[a] Measured tissue amounts are total body recovery, including intravascular, as determined by the following formulas. Measured body amount = plasma amount + (amount in intracellular + interstitial fluid for each tissue), where plasma amount = C_p [blood volume (1-HCT)]. Predicted body amount = $0.2X_{central}$ + ($0.8X_{central}$ + X_{tissue}) = intravascular + (extravascular).

minal half-life resulting in serum and tissue accumulation. This observation cannot be described by the traditional one-compartment pharmacokinetic models for aminglycoside disposition. Accumulation is difficult to detect in most patients because the small changes in peak and trough serum concentrations (Table 1) are easily obscured by assay variation. Tissue uptake (the β phase) makes only a small contribution to the initial decline in serum concentrations of tobramycin between dosing intervals. However, the continued uptake of tobramycin by most body tissues becomes readily apparent when studied by appropriately sensitive methods such as long-term urine and serum washout or autopsy analyses.

Because tobramycin has a terminal elimination half-life averaging 146 h, accumulation in tissues can be predicted to occur in every patient given the drug at commonly used dosage intervals. As previously demonstrated in rats (7), this tissue accumulation begins with the first dose.

It is apparent (Fig. 6) that patients vary greatly in the tendency to accumulate the drug in tissues, with many of these study patients retaining as much as 200 μg of drug in the tissue compartment. This study indicates that tissue uptake and release may be a major source of variation in tobramycin disposition. Further, as suggested earlier by Kunin (5), quantitation of tissue binding may become a clinically important means of discriminating differences in potential toxicity among various aminoglycoside antibiotics.

Although this model substantially revises the pharmacokinetic characterization of tobramycin disposition, it does not fully explain the variability in pharmacokinetics of the antibiotic. Besides renal function, other factors that probably contribute include changing physiological status in seriously ill patients, concurrent treatment, possible interpatient differences in the rate or extent of tissue binding, and the inherent variations present in all biological assay techniques. Finally, the renal excretion of gentamicin and probably tobramycin is sometimes affected by time and concentration-dependent flux of gentamicin between plasma, renal tissue, and urine, which can change the apparent renal clearance of the aminoglycoside antibiotic (11). However, our two-compartment pharmacokinetic model describes the rising peak and trough serum concentrations in patients undergoing therapy, explains why the drug is detected in serum and urine long after cessation of therapy, and reliably accounts for all of the drug later recovered in urine or from tissues at autopsy.

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