Accumulation Pharmacokinetics of Tobramycin

JEROME J. SCHENTAG,* GEORGE LASEZKAY, THOMAS J. CUMBO, MARTIN E. PLAUT, AND WILLIAM J. JUSKO

Departments of Pharmaceutics and Medicine, State University of New York at Buffalo, and Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York 14209

Received for publication 6 October 1977

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 (Ccr) (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\textsubscript{T}\textsuperscript{2} 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\textsubscript{T}\textsuperscript{2} 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 intramuscularly 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 \(\beta\)-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
\(\mu\)g/ml). Tissue concentrations were determined by the
prolonged elution method we have previously de-
scribed for gentamicin (11; Schentag et al., 16th
ICAAC). The tissue concentrations were multiplied by
the organ weight to determine the amount of tobra-
mycin in the organ.

**Pharmacokinetic analysis.** The decline in serum
centerations 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 com-
puter 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
centations of tobramycin as well as amounts ap-
pearing 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\textsubscript{T}\textsuperscript{2} 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\textsubscript{T}\textsuperscript{2} values. However, the
resulting serum concentrations were similar in all
three groups, reflecting that pharmacokinetic

![Table 1. Clinical comparison of 35 patients receiving tobramycin](http://aac.asm.org/)

| Parameter | C\textsubscript{T}\textsuperscript{2} group | Total dose (g) | Duration (days) | Concurrent drugs |
|-----------|-------------------------------|----------------|----------------|------------------|
| No.       | Age (yr) | Wt. (kg) | C\textsubscript{T}\textsuperscript{2} (ml/min) | 1st peak | Trough | Final trough | Hematocrit (%) |
| 1          | 0-49     | 10     | 71 ± 10 | 0.9 ± 0.1 | 1.0 ± 0.6 | 1.0 ± 0.6 |
| 2          | 50-79    | 16     | 65 ± 18 | 3.1 ± 0.3 | 2.0 ± 0.4 | 2.7 ± 0.8 |
| 3          | 80-100   | 35     | 72 ± 12 | 7.2 ± 1.4 | 2.5 ± 0.5 | 2.1 ± 0.5 |

*Values represent mean ± 1 standard deviation.
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 concentrations 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\textsubscript{Cr}. Tobramycin disposition was variable in the study patients. To illustrate the typical variability, washout serum concentrations from seven patients with widely varying C\textsubscript{Cr} values are shown in Fig. 1. First-phase half-lives generally were prolonged as C\textsubscript{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\textsubscript{c}) and steady state (V\textsubscript{dss}). The distribution and elimination parameters (\(\alpha, \beta, k_{12b}, k_{21b}, k_{elb}, Cl_B, t_{1/2b}\)) are also summarized.

Also shown in Table 2 is the predicted amount of tobramycin in the tissue compartment after the final dose (X\textsubscript{T}) and assuming dosing was continued to steady state (X\textsubscript{Teq}). 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\textsubscript{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\textsubscript{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\textsubscript{c} or ideal body weight and V\textsubscript{c}. However, our population was of similar age and few patients were markedly obese; therefore these relationships remain of interest in future
Table 2. Pharmacokinetic comparison of 35 patients receiving tobramycin

| Parameter | No. of patients | $t_{1/2a}$ (h) | $k_{12}$ (h$^{-1}$) | $k_{21}$ (h$^{-1}$) | $C_{\text{Cr}}$ (ml/min) | $V_{d1}$ (l/kg) | $V_{d2}$ (l/kg) | $V_{d3}$ (l/kg) | $C_{\text{Creatinine}}$ (ml/min) | $V_{d1}$ (l/kg) | $V_{d2}$ (l/kg) | $V_{d3}$ (l/kg) |
|-----------|----------------|----------------|-------------------|-------------------|-------------------------|----------------|----------------|----------------|---------------------------------|----------------|----------------|----------------|
| 0-40      | 10             | 0.08+0.02    | 0.06+0.01        | 0.18+0.07        | 0.06+0.06              | 0.25+0.02      | 0.44+0.07      | 0.10+0.05      | 14.7±1.9                        | 0.05+0.01      | 0.22+0.01      | 0.14+0.01      |
| 41-100    | 16             | 0.08+0.01    | 0.28+0.06        | 0.22+0.06        | 0.08+0.05              | 0.26+0.06      | 0.36+0.08      | 0.12+0.04      | 14.5±1.9                        | 0.06+0.01      | 0.26+0.01      | 0.16+0.01      |
| 101-150   | 8              | 0.18+0.09    | 0.06+0.04        | 0.06+0.04        | 0.07+0.05              | 0.22+0.01      | 0.27+0.05      | 0.11+0.00      | 14.5±1.7                        | 0.06+0.01      | 0.26+0.01      | 0.16+0.01      |
| Composite | 35             | 0.18+0.09    | 0.06+0.04        | 0.06+0.04        | 0.07+0.05              | 0.22+0.01      | 0.27+0.05      | 0.11+0.00      | 14.5±1.7                        | 0.06+0.01      | 0.26+0.01      | 0.16+0.01      |

* All values represent mean ± 1 standard deviation.

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

There was no apparent relationship between sex and $V_c$ or $V_{dss}$ 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 $C_{\text{Cr}}$ 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 $C_{\text{Cr}}$ 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 $C_C$ was usually linear, but considerable scatter was generally observed in the relationship. Our data for $k$ versus $C_C$ (Fig. 4) exhibit a linear but variable relationship between the $k$ determined from the first slope of the washout and the $C_C$ ($r = 0.76$, $P < 0.01$). 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 ($\beta$) (Fig. 4) yielded an average $\beta$ 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 $C_C$ ($r = 0.25$, $P = $ not significant).

Because neither of the individual disposition rate parameters ($k$, $\beta$) is strongly predictable by considering the influence of renal excretion alone, we also calculated the body clearance ($C_{lb}$) for each patient. Calculating the $C_{lb}$ 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 $C_{lb}$ of tobramycin averaged 66% of the $C_C$, 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 $C_C$.

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 $C_C$. 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 \( C_D \) 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 \( C_D \), 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 \( \mu g/ml \). The highest tissue concentrations were found in the kidney cortex, all of which were above 20 \( \mu g/g \). In the other patient (no. 9), the postmortem serum concentration was 5.0 \( \mu g/g \), 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.

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 \( C_D \) 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-
minal half-life resulting in serum and tissue accumulation. This observation cannot be described by the traditional one-compartment pharmacokinetic models for aminoglycoside 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.

**ACKNOWLEDGMENTS**

We thank the nursing and house staff of Millard Fillmore and Buffalo General Hospitals. We also appreciate the excellent technical assistance of D. Danner, G. Calleri, E. DeGlopper, and D. Chiarmonte.

This investigation was supported by a grant from Eli Lilly & Co. and by Public Health Service grant GM-20852 from the National Institute of General Medical Sciences.

**LITERATURE CITED**

1. Bechtol, L. D., and H. R. Black. 1975. Tobramycin in renal impairment. Am. J. Med. Sci. 269:317-321.
2. Dahlgren, J. G., E. T. Anderson, and W. L. Hewitt. 1975. Gentamicin blood levels: a guide to nephrotoxicity. Antimicrob. Agents Chemother. 8:56-62.
3. Jaffe, G., B. R. Meyers, and S. Z. Hirschman. 1974. Pharmacokinetics of tobramycin in patients with stable renal impairment, patients undergoing peritoneal dialysis, and patients on chronic hemodialysis. Antimicrob. Agents Chemother. 8:611-616.
4. Kahlmeter, G., and C. Kamme. 1975. Prolonged excretion of gentamicin in a patient with unimpaired renal function. Lancet i:296.
5. Kunin, C. M. 1970. Binding of antibiotics to tissue hemoglobin. J. Infect. Dis. 121:55-64.

| Patient no. | Time period (h) | Amt predicted (mg) | Amt measureda (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_interstitial) = intravascular + (extravascular).
6. Lalka, D., W. J. Jusko, and T. J. Bardos. 1975. Reactions of 2,2-dimethyl-aziridine type alkylating agents in biological systems. II. Comparative pharmacokinetics in dogs. J. Pharm. Sci. 65:230–235.
7. Luft, F. C., and S. A. Kleit. 1974. Renal parenchymal accumulation of aminoglycoside antibiotics in rats. J. Infect. Dis. 130:656–659.
8. Mosegaard, A., P. G. Welling, and P. O. Madsen. 1975. Gentamicin and gentamicin C1 in the treatment of complicated urinary tract infections: comparative study of efficacy, tolerance, and pharmacokinetics. Antimicrob. Agents Chemother. 7:328–332.
9. Myers, B. R., and S. Z. Hirschman. 1972. Pharmacologic studies on tobramycin and comparison with gentamicin. J. Clin. Pharmacol. 12:321–324.
10. Regamey, C., R. C. Gordon, and W. M. M. Kirby. 1973. Comparative pharmacokinetics of tobramycin and gentamicin. Clin. Pharmacol. Ther. 14:396–403.
11. Schentag, J. J., and W. J. Jusko. 1977. Renal clearance and tissue accumulation of gentamicin. Clin. Pharmacol. Ther. 22:364–372.
12. Schentag, J. J., W. J. Jusko, M. E. Plaut, T. J. Cumbo, J. W. Vance, and E. Abrutyn. 1977. Tissue persistence of gentamicin in man. J. Am. Med. Assoc. 238:327–329.
13. Siersbaek-Nielsen, K., J. M. Hansen, J. Kampmann, and M. Kristensen. 1971. Rapid evaluation of creatinine clearance. Lancet 1:1133.
14. Winters, R. E., K. D. Litwack, and W. L. Hewitt. 1971. Relation between dose and levels of gentamicin in blood. J. Infect. Dis. 124(Suppl):S90–S95.
15. Wood, M. J., and W. Farrell. 1976. Comparison of urinary excretion of tobramycin and gentamicin in adults. J. Infect. Dis. 134(Suppl):S133–S136.