ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1974, p. 611-616

Vol. 5, No. 6
Printed in U.S.A.

Pharmacokinetics of Tobramycin in Patients with Stable Renal Impairment, Patients Undergoing Peritoneal Dialysis, and Patients on Chronic Hemodialysis

GABRIEL JAFFE, BURT R. MEYERS, AND SHALOM Z. HIRSCHMAN

Division of Infectious Diseases, Department of Medicine, The Mount Sinai School of Medicine of the City University of New York, New York 10029

Received for publication 20 December 1973

The pharmacokinetics of tobramycin were studied in five patients with stable renal impairment, four patients requiring peritoneal dialysis, and four patients on chronic hemodialysis. The half-life of the drug varied with the level of the serum creatinine in the first group of patients, and the average volume of distribution was 15 liters. Only 49% of the administered dose of tobramycin was recovered during 36 h of peritoneal dialysis. The average clearance of tobramycin during hemodialysis was 49.1 ml/min, and 51.5% of the administered dose was recovered during a 6-h dialysis.

Tobramycin is a new aminoglycoside antibiotic produced by *Streptomyces tenebrarius* (1, 10, 19), with an in vitro spectrum of antibacterial activity generally similar to that of gentamicin, but with greater activity against *Pseudomonas aeruginosa* than gentamicin (3, 4, 12, 15, 22). The clinical efficacy of tobramycin for the treatment of serious gram-negative infections, including bacteremias, has been recently demonstrated (9). Although no evidence of renal toxicity or ototoxicity appeared in the 15 patients treated (9), aminoglycoside antibiotics can adversely affect vestibular, cochlear, and renal function. The toxic effects are related to both serum concentration of antibiotic and duration of therapy (8, 20). Since tobramycin is excreted mainly by the kidneys (14, 17), the dosage must be adjusted in patients with renal insufficiency in order to prevent accumulation of drug in blood and tissues, with consequent toxicity (14). In this study we investigated the pharmacokinetics of tobramycin in patients with varying degrees of renal impairment and in patients undergoing peritoneal and hemodialyses.

MATERIALS AND METHODS

Five patients with stable renal impairment, four patients undergoing peritoneal dialysis, and four patients requiring hemodialysis were studied at the Mt. Sinai Medical Center. Each patient was given a single intramuscular injection of tobramycin at a dose of 1.5 mg/kg. Serum and urine samples were collected, before injection and at timed intervals postinjection of tobramycin, from the patients with stable renal impairment and those undergoing peritoneal dialysis. Dialysate samples were collected from patients undergoing dialysis. Peritoneal dialysis with a solution of sodium chloride, calcium chloride, magnesium chloride, sodium lactate, and dextrose (Inpersol) was begun 1 h after injection of tobramycin. All dialysis runs lasted 45 to 60 min, and each patient was treated for 36 exchanges.

Patients requiring hemodialysis were placed on a Travenol coil hemodialysis machine for 6 h, 1 h after intramuscular injection of tobramycin. Arterial and venous blood samples were drawn at 1, 2, 4, and 6 h after beginning hemodialysis. No urine was produced by the patients during hemodialysis.

All serum, urine, and dialysate samples were stored at −70 C. Tobramycin concentrations were determined by the cup plate method using *Bacillus subtilis* as the test organism (7).

The regression lines of the logs of serum concentrations of tobramycin versus time, and their correlation coefficients (r), were calculated by the method of least-squares using a standard computer program to obtain the half-life (T ½) of the drug in each patient (5). The apparent volume of distribution (AVD) of tobramycin in each patient was calculated from the formula AVD = I/Co, where I is the intramuscular dose in milligrams and Co is the expected serum concentration at the time of injection, assuming rapid equilibration (5). The Co was obtained by extrapolating the regression lines of log serum concentration of tobramycin versus time (5). The clearance of tobramycin during hemodialysis was calculated from the standard formula $C = [(A - V)/A]\ Q$, where A and V are the arterial and venous concentrations of drug and Q is the flow rate. The data presented for each patient are the average values of at least two separate experiments.

All patients signed certificates of informed consent for the studies.

RESULTS

Patients with stable renal impairment. Five patients showing stable renal impairment with serum creatinine concentrations ranging from 2 to 9.3 mg/100 ml were studied (Table 1). Patients 4 and 5 received a single intramuscular injection of tobramycin the previous day within 12 h of the collection of the first serum sample. For purposes of determining the decay of tobramycin, this first serum sample was arbitrarily designated as the zero time sample. The T ½ varied from 7.7 to 70 h in these patients. The correlation coefficients (r) given in Table 1 were determined for the regression lines of the log serum concentration of tobramycin versus time. The log T ½ showed a linear correlation with the serum creatinine concentration (Fig. 1) and could be expressed by the relationship $\log y = 0.1303x + 0.649$. The mean AVD for these patients was 15 ± 1.5 (standard deviation) liters or 25.8% of body weight.

The urinary concentrations of tobramycin during the first 24 h following injection varied from 2 to 26 μg/ml (Table 1).

Patients undergoing peritoneal dialysis. Four patients with serum creatinine concentrations of 16.8 to 26.4 mg/100 ml were studied during peritoneal dialysis (Table 2). The beginning of dialysis was designated as the zero time for determining the decay of tobramycin during dialysis. Tobramycin was injected 1 h before dialysis was begun. The average concentrations of tobramycin in the dialysates varied from 0.85 μg/ml during the first 8 h to 0.66 μg/ml at 16 to 24 h and 0.34 μg/ml over the final 4 h. The total amount of tobramycin recovered in the dialysates of the patients over a 36-h period varied from 30 to 69% of the administered dose with an average recovery of 49%. The T ½ ranged from 17.5 to 37 h during dialysis. In each patient the ratio of dialysate to serum concentration of tobramycin was relatively constant throughout the dialysis, although the ratio was different in each patient (Table 3).

The urinary concentrations of tobramycin during the first 16 h following injection ranged from 3.2 to 28 μg/ml (Table 2).

Patients requiring chronic hemodialysis. The data obtained in four patients on chronic hemodialysis are given in Table 4. The beginning of hemodialysis was designated as zero time; tobramycin was injected 1 h before dialysis was begun. The amount of tobramycin removed during 6 h of hemodialysis varied from 43 to 63% of the administered dose with an average of 51.5%. The average clearance of tobramycin was 49.1 ml/min. The T ½ calculated from the serum concentrations of venous samples ranged from 2.9 to 10 h during hemodialysis.

DISCUSSION

A recent study of the effect of renal failure on the pharmacology of various drugs has shown that for most agents with a short half-life and a predominantly renal route of excretion the volume of distribution is reduced in renal failure (6). The AVD of 15 liters found in our patients with renal failure is lower than the AVD of 23 liters (30.6% of body weight) reported for tobramycin at a similar intramuscular dose in normal volunteers (16). However, the mean peak serum level of 7.55 μg/ml in our patients with stable renal impairment was higher than peak serum levels of up to 3.8 μg/ml of tobramycin determined by a similar assay, at the same dosage, previously reported in normal volunteers (11, 13, 16). The lower AVD of tobramycin in patients with renal failure may account for the higher peak serum concentrations; no correlation of serum concentration of tobramycin and hematocrit was found in a study of 15 patients (9). Simon et al. (17) reported a volume of distribution of 16.9 liters for tobramycin after a 4-h intravenous infusion at a rate of 6.6 mg/h in normal volunteers; the average T ½ was 1.6 h. Naber et al. (14) administered 1 mg of tobramycin per kg to 18 elderly males with urinary tract infections. Ten patients had serum creatinine concentrations ≤1.5 mg/100 ml, and the remaining 8 patients had concentrations of 1.5 > ≤3.8 mg/100 ml. Following intravenous administration, the average volume of distribution of tobramycin was 11.7 and 11.1 liters, respectively, in the two groups of patients. The lack of a difference in the AVD of the two groups may be due to the relatively mild impairment of renal function of most patients in the second group.

The concentrations of tobramycin in urine following an intramuscular dose of 1.5 mg/kg were greater than the minimal inhibitory concentration of the drug for most gram-negative bacteria (12) for at least the first 36 h following injection.

The correlation observed between the log of the T ½ of tobramycin and the serum creatinine concentration in our five patients with stable renal impairment requires verification with a larger number of patients. If this relationship is corroborated, then the serum creatinine could serve as a guide for tobramycin dosage in patients with impaired renal function. The serum creatinine has been suggested as a guide

TABLE 1. *Pharmacokinetics of tobramycin in patients with stable renal impairment*

Patient	Serum creatinine (mg/100 ml)	Total dose of drug (mg)	Serum concn of tobramycin (μg/ml) at times (h) postinjection										Urine concn of tobramycin (μg/ml) at intervals (h) postinjection					Total amt of tobramycin (mg) recovered in urine (% total dose) at intervals (h) postinjection					Urinary recovery of tobramycin (% total dose)	Serum T ½ (h)[b]
			0	1	2	4	6	8	12	24	36	48	0-0	8-16	16-24	24-32	32-36	0-8	8-16	16-24	24-32	32-36		
1	2.0	75		10.0	7.6	7.6	5.2			0.64	0.54 (33)[a]	0.15	56	26.7	16.0	17 (24-48)[a]	7 (48-72)[a]	26.2 (34.9%)	11.1 (14.8%)	6.5 (8.6%)	23.0 (24-48)[a] (30.6%)	6.65 (48-72)[a] (8.8%)	97.7	7.72 (r = −0.98)
2	2.9	103.5		3.45	4.2	4.2		2.7	2.2	0.85	0.56		5.0	4.2	2.05	0.93	2.6	3.28 (3.1%)	3.14 (3.0%)	1.73 (1.67%)	0.45 (0.4%)	0.94 (0.9%)	9.0	10.98 (r = −0.99)
3	6.4	82.5		5.9	5.9	5.0		3.3	3.7	2.9	2.5		6.4 (0-12)[a]		4.0 (12-24)[a]			3.5 (0-12)[a] (4%)	3.5 (12-24)[a] (4%)				8	33.44 (r = −0.89)
4	7.8	87	2.9[c]						2.7 (18)[a]			1.1 (66)[a]												44.93 (r = −0.98)
5	9.3	100	4.7[c]						4.1 (18)[a]			3.1 (42)[a]												70.00 (r = −0.99)

[a] Time (h) of sample postinjection.
[b] r, correlation coefficient.
[c] Patient had received tobramycin the previous day; first sample for serum concentration was arbitrarily called zero time.

TABLE 2. *Pharmacokinetics of tobramycin in*

Patient	Serum creatinine (mg/100 ml)	Total dose drug (mg)	Serum concn of tobramycin (μg/ml) at times (h) after beginning dialysis									Urine concn of tobramycin (μg/ml) at intervals (h) after beginning dialysis				Total amt of tobramycin (mg) recovered in urine (% total dose) at intervals (h) after beginning dialysis			
			0	1	2	4	6	8	12	24	36	0-8	8-16	16-24	24-32	0-8	8-16	16-24	24-32
1	16.8	94.5	3.4	6.6	4.8	6.3		5.0	4.8	3.6	2.9	11.0	12.0	11.5	7.0	0.27 (.28%)	0.65 (.68%)	0.23 (.24%)	0.14 (.14%)
2	19.2	87		4.3	5.1	3.9	3.6	2.7	2.7	1.9	1.1	3.2	7.6		2.9	0.48 (.55%)	0.68 (.78%)		0.22 (.25%)
3	23.5	82.5	7.2	7.6		7.6	5.6		3.5 (18)[b]	4.2	4.2 (40)[b]	28.0	24.0	24.0					
4	26.4	120	13.5	17.5	12.0	15.5	12.0	14.0	13.0	7.6		9.0		11.0 (24-32)[b]	13.0 (32-40)[b]	1.71 (1.42%)		1.65 (24-32)[b] (1.37%)	2.08 (32-40)[b] (1.73%)

[a] *r*, correlation coefficient.
[b] Time (h) or sample.

for gentamicin dosage in patients with renal dysfunction (2). The serum creatinine concentration is more easily obtained by the physician than a creatinine clearance determination. Naber et al. (14) were able to correlate the tobramycin T ½ and serum creatinine concentration by the equation $y = 1.79x + 0.8$ ($r = 0.82$). They further suggested that the correlation could be simplified to $y = 2x$. Thus, if tobramycin were given every third T ½, the dosage interval (h) in renal failure for a dose of 1 mg/kg could be approximated by multiplying the serum creatinine by 6. However, the patients studied by Naber et al. (14) had serum creatinine concentrations ≤3.8 mg/100 ml, and our data suggest that such simplified correlations may not hold at higher creatinine concentrations.

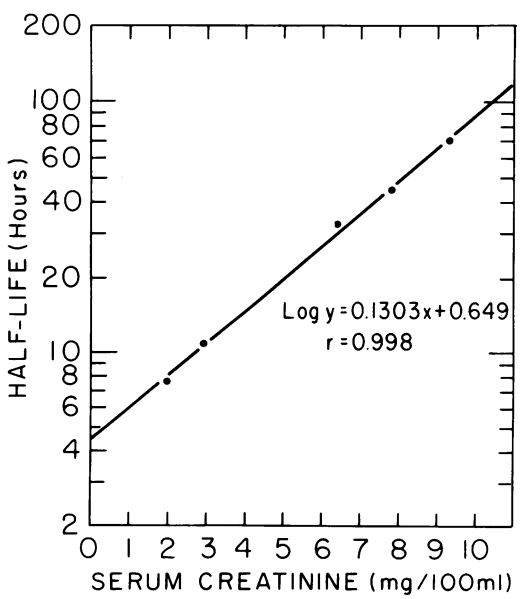

FIG. 1. *Correlation of serum half-life of tobramycin and serum creatinine concentration in patients with stable renal impairment.*

Tobramycin was slowly removed by peritoneal dialysis. The T ½ during peritoneal dialysis differed for the four patients. The factors determining the exchange of tobramycin across the peritoneal membranes in a patient are not yet known. The concentrations of tobramycin in the dialysate returns were lower than the minimal inhibitory concentrations of the drug for most gram-negative bacteria (12). Weinstein et al. (21) found low concentrations of tobramycin in peritoneal dialysate returns in the single patient they studied and suggested that patients with peritonitis may require intraperitoneal instillation of tobramycin in order to achieve therapeutic levels. Low concentrations of gentamicin also have been found in peritoneal dialysates (18). In contrast, the urinary concentrations of tobramycin in the patients undergoing peritoneal dialysis exceeded the minimal inhibitory concentration of the drug for most gram-negative urinary pathogens.

During 6 h of hemodialysis an average of 51% of the administered dose of tobramycin was removed in our patients. Using a Kiil artificial kidney, Lockwood and Bower (11) reported 70% removal of tobramycin during a 12-h dialysis. The serum T ½ of tobramycin decreased 7-fold during hemodialysis. The T ½ of tobramycin of patient 4 during hemodialysis was much shorter than the T ½ of the other three patients (Table 4). Although the explanation for this finding is not apparent, it should be noted that a 6-h venous sample was not available for this patient. The average clearance of tobramycin determined from our patients was 49.1 ml/min.

patients undergoing peritoneal dialysis

Dialysate concn of tobramycin (μg/ml) at intervals (h) after beginning dialysis					Total amt of tobramycin (mg) recovered in dialysates (% total dose) at intervals (h) after beginning dialysis					Percentage of total dose recovered in urine	Percentage of total dose recovered in dialysates	Serum T ½ (h)[a]
0–8	8–16	16–24	24–32	32–36	0–8	8–16	16–24	24–32	32–36			
0.87	0.75	0.61	0.37	0.42	10.27 (10.86%)	8.05 (8.51%)	7.49 (7.92%)	4.6 (4.86%)	2.65 (2.8%)	1.34	34.95	37.16 (r = −0.93)
1.08	0.77	0.63	0.58	0.35	22.2 (25.5%)	15.8 (18.2%)	7.66 (8.8%)	8.31 (9.6%)	2.82 (3.24%)	1.58	65.34	17.5 (r = −0.98)
0.72	0.60	0.68	0.50	0.24	19.12 (23%)	11.08 (13%)	13.93 (16%)	9.25 (11%)	5.11 (6%)		69	21.8 (r = −0.89)
0.72	0.84	0.74	0.41 (24–27)[b]		9.18 (7.7%)	12.32 (10.3%)	11.93 (9.9%)	2.82 (24–27)[b] (2.4%)		2.8	30.3	25.1 (r = −0.85)

TABLE 3. *Ratios of dialysate and serum concentrations of tobramycin in patients undergoing peritoneal dialysis*

Patient	Concn dialysate/concn serum (%) at intervals (h) after beginning dialysis					Average ratio (%)	Percentage of total dose recovered in dialysate
	0–8	8–16	16–24	24–32	32–40		
1	16	15	16	16	15	16	34.95
2	27	28	28	38	29	30	65.34
3	10	13	17	10	5	11	69
4	5	6	7	6 (24–27)[a]		6	30.3
Avg for 4 patients						16	49.4

[a] Time interval (h) of sample.

TABLE 4. *Pharmacokinetics of tobramycin in patients on hemodialysis*

Patient	Serum creatinine (mg/100 ml)	Total dose of tobramycin (mg)	Concn of tobramycin (μg/ml) in sera of arterial (A) and venous (V) blood at times (h) after beginning dialysis									Percentage of total dose removed by dialysis	Average clearance (ml/min) of tobramycin	Serum T ½ (h)[a]
			0	1		2		4		6				
			V	A	V	A	V	A	V	A	V			
1	7.8	87	6.0	5.5	5.5	4.5	4.4	3.7	3.3	4.2	2.9	52	65.2	7.72 (r = −0.89
2	9.3	100	9.0	7.3	4.7	8.8	6.7	6.7	5.8	6.1	4.7	48	52.2	10.00 (r = −0.61)
3	15.7	90	5.6			4.5	3.6	3.3	3.4	3.6	3.2	43	31.0	6.36 (r = −0.98)
4	19.2	72	9.6	8.2	6.4	7.6	4.2	6.2	3.6			63	47.9	2.90 (r = −0.93)

[a] r, correlation coefficient.

A clearance of 58.8 ml/min was found by Lockwood and Bower using a Kiil artificial kidney (11).

ACKNOWLEDGMENTS

This work was supported by Public Health Service grant no AI-00410 from the National Institute of Allergy and Infectious Diseases and a grant from the Eli Lilly Research Laboratories.

The authors are grateful for the expert technical assistance of Virginia Funke and Ilona Kovacs.

LITERATURE CITED

1. Black, H. R., and R. S. Griffith. 1971. Preliminary studies with nebramycin factor 6, p. 314-321. Antimicrob. Ag. Chemother. 1970.
2. Cutler, R. E., A. M. Gyselynek, W. P. Fleet, and A. W. Forrey. 1972. Correlation of serum creatinine concentration and gentamicin half-life. J. Amer. Med. Ass. **219**:1037-1041.
3. Del Bene, V. E., and W. E. Farrar. 1972. Tobramycin. In vitro activity and comparison with kanamycin and gentamicin. Antimicrob. Ag. Chemother. **1**:340-342.
4. Dienstag, J., and H. C. Neu. 1972. In vitro studies of tobramycin, an aminoglycoside antibiotic. Antimicrob. Ag. Chemother. **1**:41-45.
5. Dost, F. H. 1968. Grundlagen der Pharmakokinetik, p. 36, 238, 275, 311. Georg Thieme Verlag, Stuttgart.
6. Gibaldi, M., and D. Perrier. 1972. Drug distribution and renal failure. J. Clin. Pharmacol. **12**:201-204.
7. Grove, D. C., and W. A. Randall. 1955. Assay methods of antibiotics: a laboratory manual. Medical Encyclopedia, Inc., New York.
8. Jackson, G. G., and G. Arcieri. 1971. Ototoxicity of gentamicin in man: a survey and controled analysis of clinical experience in the United States. J. Infect. Dis. **124 (suppl.)**:130-137.
9. Jaffe, G., W. Ravreby, B. R. Meyers, and S. Z. Hirschman. 1974. A clinical study of the use of the new aminoglycoside tobramycin for therapy of infections due to gram-negative bacteria. Antimicrob. Ag. Chemother. **5**:75-81.
10. Koch, R. F., and J. A. Rhoades. 1971. Structure of nebramycin factor 6, a new aminoglycosidic antibiotic, p. 309-313. Antimicrob. Ag. Chemother. 1970.
11. Lockwood, W. R., and J. D. Bower. 1973. Tobramycin and gentamicin concentrations in the serum of normal and anephric patients. Antimicrob. Ag. Chemother. **3**:125-129.
12. Meyers, B. R., and S. Z. Hirschman. 1972. Tobramycin: in vitro antibacterial spectrum of a new aminoglycoside. J. Clin. Pharmacol. **12**:313-320.
13. Meyers, B. R., and S. Z. Hirschman. 1972. Pharmacologic studies on tobramycin and comparison with gentamicin. J. Clin. Pharmacol. **12**:321-324.
14. Naber, K. G., S. R. Westernfelder, and P. O. Madsen. 1973. Pharmacokinetics of the aminoglycoside antibiotic tobramycin in humans. Antimicrob. Ag. Chemother. **3**:469-473.
15. Preston, D. A., and W. E. Wiek. 1971. Preclinical assessment of the antibacterial activity of nebramycin factor 6, p. 322-327. Antimicrob. Ag. Chemother. 1970.
16. Regamy, C., R. C. Gordon, and W. M. M. Kirby. 1973. Comparative pharmacokinetics of tobramycin and gentamicin. Clin. Pharmacol. Ther. **14**:396-403.
17. Simon, V. K., E. U. Mösinger, and V. Malercsy. 1973. Pharmacokinetic studies of tobramycin and gentamicin. Antimicrob. Ag. Chemother. **3**:445-450.
18. Smithivas, T., P. J. Hyams, R. Matalon, M. S. Simberkott, and J. J. Rahal. 1971. The use of gentamicin in peritoneal dialysis. I. Pharmacologic results. J. Infect. Dis. **124 (suppl.)**:77-83.
19. Stark, W. M., M. M. Hoehn, and N. G. Knox. 1968. Nebramycin, a new broad spectrum antibiotic complex. I. Detection and biosynthesis, p. 314-323. Antimicrob. Ag. Chemother. 1967.
20. Waitz, J. A., E. L. Moss, and M. J. Weinstein. 1971. Aspects of the chronic toxicity of gentamicin sulfate in cats. J. Infect. Dis. **124(suppl.)**:130-137.
21. Weinstein, A. J., A. W. Karchmer, and R. C. Moellering. 1973. Tobramycin concentrations during peritoneal dialysis. Antimicrob. Ag. Chemother. **4**:432-434.
22. Wick, W. E., and J. S. Welles. 1968. Nebramycin, a new broad spectrum antibiotic complex. IV. In vitro and in vivo laboratory evaluation, p. 341-348. Antimicrob. Ag. Chemother. 1967.