ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1973, p. 125-129

Vol. 3, No. 1
Printed in U.S.A.

Tobramycin and Gentamicin Concentrations in the Serum of Normal and Anephric Patients

W. R. LOCKWOOD AND JOHN D. BOWER

Department of Medicine and the Artificial Kidney Unit of the University of Mississippi Medical Center and the Veterans Administration Center, Jackson, Mississippi 39216

Received for publication 30 October 1972

The serum half-life of tobramycin was found to be the same as that of gentamicin in patients with similar renal function. The values ranged from 2 hr in normal volunteers to 53.4 hr in anephric patients. Both drugs were readily removed from the serum by the Kiil artificial kidney, with a 70% reduction in serum concentrations during a 12-hr dialysis period.

The aminoglycoside antibiotic tobramycin has in vitro antibacterial activity similar to that of gentamicin (2, 6, 7, 9, 11, 13, 15, 17, 18). Although most observers have found that the new agent is more active than gentamicin against *Pseudomonas*, one report indicated that *Pseudomonas* isolates resistant to gentamicin were resistant to tobramycin also (3). Nevertheless, the new agent shows considerable promise as an alternative to gentamicin or the polymyxins in the treatment of many serious infections.

Several reports have dealt with the levels of gentamicin that are found in the serum of both normal individuals and patients with impaired renal function (1, 4, 5, 8-10, 12, 14). Data on tobramycin (14) are limited in this area, and there are no reports on studies in anephric individuals or patients with impaired renal function. Both tobramycin and gentamicin are excreted in the urine, and both are known to have nephrotoxicity and ototoxicity that are related to the serum concentrations of the agent in use or to the duration of therapy, or to both. It is necessary, therefore, to reduce the daily dose of the drugs in the presence of renal impairment. In this regard, several studies have provided data for gentamicin on the relation between the extent of renal impairment, as measured by the creatinine clearance, and the concentrations in the serum after injection of the drug (1, 4, 5, 8, 12). It was the purpose of our study to compare the serum half-lives ($T_{1/2}$) of tobramycin and gentamicin in normal volunteers and in patients with impaired or no renal function and to compare our results (presented in part at the 12th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N.J., 27 September 1972) with those previously published for gentamicin.

MATERIALS AND METHODS

Normal subjects. Ten freshmen or sophomore medical students served as paid subjects. Each had a normal urinalysis, a normal serum creatinine, and a diastolic blood pressure less than 90 mm of mercury. After collection of a sample of venous blood, 100 mg of the drug being studied was injected into the deltoid muscle. Additional venous samples were collected at 0.5, 1, 2, 4, and 6 hr after the injection

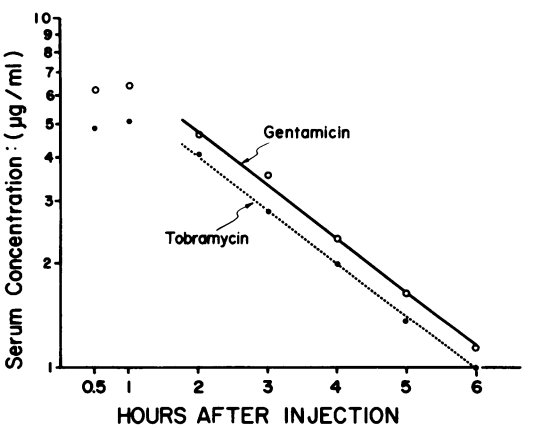

FIG. 1. *Semilogarithmic plots of the average drug concentrations in the serum of normal subjects after 100-mg intramuscular doses of tobramycin (●) and gentamicin (○), indicating half-lives of 2 hr for each drug in adults with normal kidneys.*

TABLE 1. *Drug concentrations in the serum of healthy adults after a 100-mg intramuscular dose*

Patient no.	Drug	Antibiotic concn in serum (μg/ml)						
		0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
1	Tobramycin	8.2	7.5	6.7	3.7	2.6	1.7	1.2
	Gentamicin	7.5	7.8	5.4	3.7	2.5	1.9	1.4
2	Tobramycin	4.8	5.6	4.0	2.5	1.6	1.0	<1
	Gentamicin	5.4	4.9	3.5	2.4	1.4	1.1	0.7
3	Tobramycin	5.2	5.8	4.2	2.5	1.8	1.2	<1
	Gentamicin	4.9	4.9	3.7	3.0	2.2	1.3	<1
4	Tobramycin	3.8	3.4	3.4	2.5	1.6	1.3	1.0
	Gentamicin	5.9	6.0	4.9	4.5	2.9	2.2	<1
5	Tobramycin	6.0	5.1	3.4	2.6	1.8	1.1	<1
	Gentamicin	7.7	7.3	4.9	2.9	1.9	1.5	1.0
6	Tobramycin	3.4	3.9	4.0	2.8	1.8	1.3	<1
	Gentamicin	6.5	7.3	5.5	4.7	3.7	2.3	1.6
7	Tobramycin	6.0	6.0	4.2	3.2	2.4	1.8	<1
	Gentamicin	8.0	7.7	6.1	4.2	2.6	1.8	1.4
8	Tobramycin	2.5	3.1	3.3	2.5	2.3	1.4	1.4
	Gentamicin	5.0	6.5	5.3	4.3	N.D.	N.D.	N.D.
9	Tobramycin	3.0	4.3	4.6	3.3	2.5	1.9	1.3
	Gentamicin	6.7	6.3	4.2	3.1	2.1	1.6	1.3
10	Tobramycin	5.4	6.0	3.3	2.7	1.7	1.0	<1
	Gentamicin	5.2	5.5	3.7	3.1	1.9	1.3	0.95
Mean	Tobramycin	4.83	5.07	4.11	2.83	2.01	1.37	<1
	Gentamicin	6.33	6.42	4.72	3.59	2.35	1.66	1.15

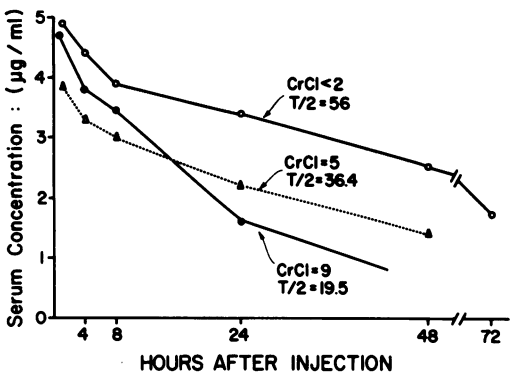

FIG. 2. *Comparison of tobramycin concentrations in the serum of three individuals with impaired renal function.*

via an indwelling needle. After each sample was drawn, the needle was flushed with a small volume of heparin in 0.9% NaCl to prevent clots from obstructing the bore. A 2-ml blood sample was withdrawn into a syringe used only for this purpose prior to collection of the sample for antibiotic analysis in a disposable syringe used only once. The blood was allowed to clot at room temperature, and the serum was removed and frozen at −15 C until the day of the assay. In all instances, the tobramycin study was done first, and at least 1 week elapsed prior to the gentamicin study.

Impaired renal function. Three patients with poor renal function were available for study on the wards of the University Hospital. Each received one injection of tobramycin, and serum samples were obtained at intervals over a 48- or 72-hr period (Fig. 2).

Anephric subjects. Five surgically anephric patients of the artificial kidney unit were chosen for study. They were all free from infection at the time of the study and were not receiving any other antibiotics. After intramuscular injection of 50 mg of the drug under study, blood samples were collected from the indwelling arteriovenous shunt at 2, 4, 8, 24, 48, and, when possible, 72 hr. A second dose of 50 mg was then injected intramuscularly, and 1 hr later a sample of blood was collected. The dialysis procedure was then started, and at 2 and 4 hr samples were collected simultaneously from the arterial and venous lines and the flow through the artificial kidney was measured in triplicate. As with the normal individuals, the tobramycin study was done first. At least 4 weeks elapsed prior to the gentamicin study. One of the anephric patients received a transplanted kidney after the tobramycin study and was not available for the gentamicin study. All samples were allowed to clot and the serum was frozen as in the cases of the normal subjects.

Antibiotic assay. The antibiotic concentrations in the serum samples were measured by the technique of Sabath et al. with the use of spores of *Bacillus subtilis* ATCC 6633 in heart infusion agar (16).

RESULTS

Normal subjects. Drug concentrations in the serum of normal subjects rose sharply after the injections and reached a peak at 1 hr (Table 1). The average value for tobramycin at that

TABLE 2. *Drug concentrations in the serum of anephric patients after a 50-mg dose*

Patient no.	Drug	Antibiotic concn in serum (μg/ml)						
		1 hr	2 hr	4 hr	8 hr	24 hr	48 hr	72 hr
1	Tobramycin	4.5	3.7	4.9	3.7	3.3	2.5	—
	Gentamicin	4.7	5.1	4.7	4.1	3.1	2.3	—
2	Tobramycin	3.0	3.2	3.0	2.6	2.0	1.9	—
	Gentamicin	2.8	3.3	2.6	2.5	1.9	1.9	—
3	Tobramycin	4.4	3.8	3.5	3.4	2.5	1.8	1.5
	Gentamicin	5.5	4.8	4.8	3.8	2.8	1.4	1.3
4	Tobramycin	3.5	5.4	2.9	2.7	1.9	1.4	<1
	Gentamicin	4.0	4.2	3.6	2.8	2.3	—	1.2
5	Tobramycin	3.6	3.5	3.2	3.1	2.6	2.0	1.7
	Gentamicin							
Mean	Tobramycin	3.8	3.5	3.5	3.1	2.5	1.9	1.3
	Gentamicin	4.3	4.4	3.9	3.3	2.5	1.9	1.3

point was 5.1 μg/ml, slightly less than that for gentamicin, which was 6.4 μg/ml. This difference is significant ($P < 0.05$) by the t test for nonindependent variables. The average values then decreased as a first-order decay function, and at 6 hr both drugs showed levels of approximately 1 μg/ml. Semilogarithmic plots (Fig. 1) yielded straight lines after 1 hr, and the slope was minus two for both drugs, indicating a T½ of 2 hr, as previously reported (14).

Impaired renal function. The three subjects with impaired renal function had creatinine clearances of 9, 5, and less than 2 ml per min. The tobramycin T½ was 19.5, 36.4, and 56 hr, respectively (Fig. 2). We were unable to study the concentrations of gentamicin in the serum of these patients, but the tobramycin concentrations are in good agreement with predicted values for gentamicin on the basis of previously reported data. McHenry et al. (12) gave values of 23 and 38 hr for the second and third individuals, and Gingell and Waterworth (8) reported 11 and 35 hr, respectively. The patient with the creatinine clearance of less than 2 was, in effect, anephric, and the T½ of 56 hr is in good agreement with our own findings in anephric subjects (*see below*).

Anephric patients. The average drug concentrations in the serum of anephric patients at 1 hr were 3.8 μg/ml for tobramycin and 4.3 μg/ml for gentamicin (Table 2). The difference is not significant. Semilogarithmic plots (Fig. 3) of the average values again gave straight lines after the initial peak, and in this instance the lines were superimposed. The negative slope indicated a T½ of 53.4 hr.

Removal by the Kiil artificial kidney. The average concentration of tobramycin prior to dialysis was 4.7 μg/ml, and the level was reduced to 1.5 μg/ml by the end of the 12-hr dialysis period (Table 3). Similarly, the average gentamicin concentration of 5.3 μg/ml was reduced to 1.6 μg/ml (Table 3). The figures indicate reductions to 32 and 30% of the starting levels (Fig. 4). The 2% difference is not significant.

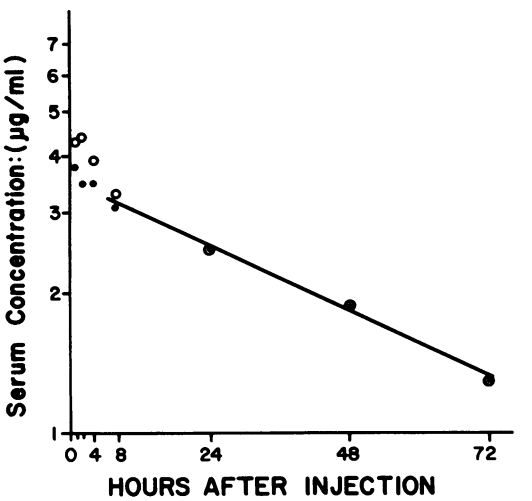

FIG. 3. *Semilogarithmic plots of average drug concentrations in the serum of anephric patients after 50-mg intramuscular doses of tobramycin (●) and gentamicin (○). The lines are superimposed and indicate identical half-lives of 53.4 hr.*

The Kiil artificial clearance was determined on the basis of 10 sets of observations for tobramycin and 7 for gentamicin by use of the formula $(A - V)/A \times$ flow rate (Table 4). The value for tobramycin was 58.8 ml/min, and that for gentamicin was 42.1 ml/min. The difference in these findings is not significant, but the $A - V$ values are small, and the inherent inaccuracies of the procedure create large standard deviations.

TABLE 3. *Serum concentrations before and after 12-hr dialysis with a Kiil artificial kidney*

Patient no.	Drug	Antibiotic concn in serum (μg/ml)	
		Pre-dialysis	Post-dialysis
1	Tobramycin	6.0	1.9
	Gentamicin	5.8	1.9
2	Tobramycin	4.4	1.7
	Gentamicin	5.0	1.5
3	Tobramycin	4.6	<1
	Gentamicin	4.8	<1
4	Tobramycin	2.9	1.3
	Gentamicin	5.7	2.1
5	Tobramycin	5.4	1.6
	Gentamicin	ND[a]	ND
Mean	Tobramycin	4.7	1.5
	Gentamicin	5.3	1.6

[a] Not determined.

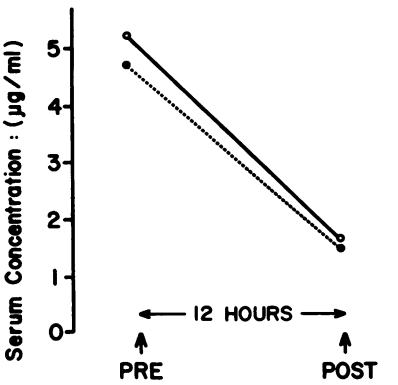

FIG. 4. *Comparison of average drug concentrations in the serum of anephric adults before and after dialysis. Approximately 70% reduction in the drug levels occurred during a 12-hr period of dialysis.*

TABLE 4. *Simultaneous measurements of arterial and venous concentrations and the calculated clearance by a Kiil artificial kidney*[a]

Patient no.	Drug	2 hr			4 hr		
		Arterial concn (μg/ml)	Venous concn (μg/ml)	Clearance (ml/min)	Arterial concn (μg/ml)	Venous concn (μg/ml)	Clearance (ml/min)
1	Tobramycin	5.3	3.3	60.8	3.3	2.5	48.5
	Gentamicin	4.2	4.7	—	4.0	3.0	34.7
2	Tobramycin	3.6	3.2	46.3	3.0	2.5	34.9
	Gentamicin	3.7	3.4	30.5	3.1	2.0	62.8
3	Tobramycin	3.4	2.4	59.5	2.8	1.7	65.6
	Gentamicin	3.3	2.4	48.6	2.6	1.6	66.2
4	Tobramycin	2.8	2.8	22.2	3.5	2.5	125.0
	Gentamicin	2.7	2.6	5.29	2.1	1.9	46.6
5	Tobramycin	4.2	2.5	66.6	3.1	1.9	58.8
	Gentamicin						
Mean	Tobramycin	3.9	3.2	—	3.1	2.2	—
	Gentamicin	3.5	3.3	—	3.0	2.1	—

[a] Mean clearance: tobramycin (10 observations), 58.8 ml/min; gentamicin (7 observations), 42.1 ml/min.

DISCUSSION

The data reported herein show that the new drug tobramycin and the established agent gentamicin have virtually identical serum half-lives in patients with similar renal function, ranging from 2 hr in the normal to 53.4 hr in the anephric state. Likewise, the two agents are removed at about the same rate by the Kiil artificial kidney. The clinician is, therefore, able to predict with reasonable accuracy, using data already published, a dose of tobramycin that can be expected to give safe serum concentrations at all levels of renal function. Caution is suggested in using such predicted doses, and the use of serum antibiotic assays is urged.

Hemodialysis readily removed both agents from the blood. The results of our studies indicated that approximately 70% of the drug was removed by a 12-hr dialysis procedure. Clearly, if toxic levels occur as a result of overdosage, hemodialysis provides a method of removing the unwanted drug. However, to maintain therapeutic levels in the anephric patient, an injection of the drug must be administered after each dialysis period.

ACKNOWLEDGMENTS

We are indebted to Mary E. Duffy, Betty Preston, and Gordon B. Strom, Jr., for their assistance.

This work was supported by a grant from Eli Lilly & Co.

LITERATURE CITED

1. Altmann, G., B. Bogokowsky, G. Boner, and H. E. Eliahou. 1970. Blood levels of ampicillin, kanamycin and gentamicin in the uremic patient. Israel J. Med. Sci. **6**:683-690.
2. Black, H. R., and R. S. Griffith, 1971. Preliminary studies with nebramycin factor 6. Antimicrob. Ag. Chemother. 1970, p. 314-321.
3. Brusch, J. L., M. Barza, M. G. Bergerson, and L. Weinstein. 1972. Cross resistance of *Pseudomonas* to gentamicin and tobramycin. Antimicrob. Ag. Chemother. **1**:280-281.
4. Curtis, J. R., S. J. McDonald, and J. H. Weston. 1967. Parenteral administration of gentamicin in renal failure: patients undergoing intermittent haemodialysis. Brit. Med. J. **2**:537-539.
5. Cutler, R. E., A. M. Gyselynck, P. Fleet, and A. W. Forrey. 1972. Correlation of serum creatinine concentrations and gentamicin half-life. J. Amer. Med. Ass. **219**:1037-1011.
6. Del Bene, V. E., and W. E. Farrar, Jr. 1972. Tobramycin: in vitro activity and comparisons with kanamycin and gentamicin. Antimicrob. Ag. Chemother. **1**:340-342.
7. Dienstag, J., and H. C. Neu. 1972. In vitro studies of tobramycin, an aminoglycoside antibiotic. Antimicrob. Ag. Chemother. **1**:41-45.
8. Gingell, J. C., and P. M. Waterworth. 1968. Dose of gentamicin in patients with normal renal function and renal impairment. Brit. Med. J. **2**:19-22.
9. Klein, J. O., T. C. Eickhoff, and M. Finland. 1964. Gentamicin: activity in vitro and observations in 26 patients. Amer. J. Med. Sci. **248**:528-543.
10. Kunin, C. M. 1967. A guide to use of antibiotics in patients with renal disease. A table of recommended doses and factors governing serum levels. Ann. Intern. Med. **67**:151-158.
11. Levison, M. E., R. Knight, and D. Kaye. 1972. In vitro evaluation of tobramycin, a new aminoglycoside antibiotic. Antimicrob. Ag. Chemother. **1**:381-384.
12. McHenry, M. C., T. L. Gavan, R. W. Gifford, N. A. Geurkink, R. A. van Ommen, M. A. Town, and J. G. Wagner. 1971. Gentamicin dosages for renal insufficiency. Adjustments based on endogenous creatinine clearance and serum creatinine concentration. Ann. Intern. Med. **74**:192-197.
13. Meyer, R. D., L. S. Young, and D. Armstrong. 1971. Tobramycin (nebramycin factor 6): in vitro activity against *Pseudomonas aeruginosa*. Appl. Microbiol. **22**:1147-1151.
14. Meyers, B. R., and S. Z. Hirschman. 1972. Pharmacologic studies on tobramycin and comparison with gentamicin. J. Clin. Pharmacol. **12**:321-324.
15. Preston, D. A., and W. E. Wick. 1971. Preclinical assessment of the antibacterial activity of nebramycin factor 6. Antimicrob. Ag. Chemother. 1970, p. 322-327.
16. Sabath, L. D., J. I. Causey, P. A. Ruch, L. L. Stumpf, and M. Finland. 1971. Rapid microassay for circulating nephrotoxic antibiotics. Antimicrob. Ag. Chemother. 1970, p. 83-90.
17. Shadomy, S. and C. Kirchoff. 1972. In vitro susceptibility testing with tobramycin. Antimicrob. Ag. Chemother. **1**:412-416.
18. Traub, W. H., and Raymond, E. A. 1972. Evaluation of the in vitro activity of tobramycin compared with that of gentamicin sulfate. Appl. Microbiol. **23**:4-7.