Therapy of *Pseudomonas aeruginosa* Infections with Tobramycin

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The efficacy of tobramycin in doses of 2.7 to 5.6 mg/kg per day in 29 courses of therapy in 25 hospitalized patients with serious *Pseudomonas aeruginosa* infections was studied. Eighty-three percent of the *P. aeruginosa* strains showed zones of inhibition of 16 mm or more around a 10- μ g tobramycin disk in the Bauer-Kirby disk method. Tobramycin minimal inhibitory concentration ranged from <0.05 to 1.5 μ g/ml (microtiter twofold dilution method); for gentamicin they ranged from 0.05 to 6.2 μ g/ml; corresponding geometric means were 0.19 and 0.49 μ g/ml. Therapy was given for a median of 10 days (mean 19, range 1 to 83). The clinically satisfactory response rate for the 29 courses of therapy was 52%: critically ill, 44%; seriously ill, 50%; moderately ill, 80%. The response rates for various sites of infection were bone and cartilage, 100%; urinary tract infection, 56%; wound, 50%; respiratory tract, 67%; septicemia, 40%; abscess, 0%; burns, 44%. No adverse reactions were seen. Serum concentration (μ g/ml $\pm$ standard deviation) of tobramycin determined by an agar-well plate method, were 4.81 ± 2.17 (1 h); 3.24 ± 1.43 (2 h); 2.35 ± 1.30 (4 h); and 1.40 ± 1.09 (8 h). Tobramycin appears to be as efficacious as gentamicin in the treatment of serious *P. aeruginosa* infections and has a theoretical advantage of lower minimal inhibitory concentration for *P. aeruginosa*. The data suggest that, for life-threatening infections, dosages of tobramycin may need to be increased over those used in this study.

Serious infections due to *Pseudomonas aeruginosa* have become increasingly frequent in recent years. Two factors responsible for this rise are the increasing numbers of immunologically compromised patients, and the frequent use of potent antibiotics which suppress or eliminate sensitive bacteria, thus favoring the growth of *Pseudomonas* (12). Gentamicin and carbenicillin have been the most effective antibiotics for *Pseudomonas* infections but strains resistant to one or both have emerged (6). Tobramycin, an aminoglycoside chemically similar to gentamicin, has been shown to possess a greater in vitro effectiveness against *P. aeruginosa*. For most strains of *Pseudomonas*, the minimal inhibitory concentrations (MIC) of tobramycin frequently have been slightly less than that of gentamicin (2, 3, 11, 13, 19). However, few data on the clinical efficacy of tobramycin have yet been published (8, 9). We have investigated the efficacy of tobramycin in 25 hospitalized patients with serious infections caused by *P. aeruginosa*.

MATERIALS AND METHODS

After informed consent was obtained, tobramycin at a dose of 2.7 to 5.6 mg/kg per day was administered to 25 University of Michigan Medical Center hospitalized patients between April 1972 and September 1973. Loading doses were not administered. *P. aeruginosa* had been isolated from each patient admitted to the study and was considered the primary pathogen in each case. All bacteria were cultured and identified in the Clinical Microbiology Laboratory using standard techniques. Tobramycin and gentamicin disk diffusion sensitivities were performed by the Bauer-Kirby technique using 10- μ g disks (1). MIC and bactericidal (MBC) concentrations of tobramycin and gentamicin were determined in the research laboratories of the Infectious Disease Division by microtiter methods using twofold dilutions in Mueller-Hinton broth (6, 7).

Fifteen of the 25 patients (60%) were moribund on admission to the study and were classified as critically ill. Five more were seriously ill, but were not thought to be moribund initially; five were moderately ill. Two patients (no. 2 and 17) received two courses of tobramycin; one patient (no. 9) received three courses. Twenty patients received other antibiotics

concomitantly for at least part of their tobramycin course: carbenicillin, cephalosporins, chloramphenicol, clindamycin, methicillin, penicillin G, tetracycline, amphotericin B, isoniazid, and ethambutol. Clinical results were judged satisfactory if the patient clinically improved, with elimination or significant abatement of symptomatology and signs. Bacteriological response was considered satisfactory if *P. aeruginosa* could not be cultured from the original site of infection after therapy; or, in the case of urinary tract infections, if the organism was reduced to insignificant numbers. The bacteriologically unsatisfactory response group included, in addition to courses of therapy in which the pathogen persisted or recurred, those in which therapy was discontinued prematurely, either inadvertently or due to death of the patient.

Hemoglobin, hematocrit, white blood count and differential, urinalysis, blood urea nitrogen, serum creatinine, creatinine clearance, platelet count, prothrombin time, bilirubin, alkaline phosphatase, serum glutamic pyruvic transaminase, and serum glutamic oxaloacetic transaminase were obtained before, during, and after tobramycin therapy whenever possible. Similarly timed audiometry was performed when patients were able to cooperate. The assay of serum concentrations of tobramycin (after 48 h of treatment) was performed using the agar well plate method of Winters et al. which was modified by the replacement of *Bacillus globigii* with *B. subtilis* spores (20). Cephalosporinase and/or penicillinase were added to serum specimens from patients receiving cephalosporins, carbenicillin, and penicillin G. Tobramycin serum levels of patients who were also receiving chloramphenicol, clindamycin, tetracycline, or methicillin could not be determined by our bioassay and are not included in this report.

When bacteria other than *P. aeruginosa* were isolated (19 of 25 patients), and seemed implicated as pathogens, appropriate antibiotics were added as indicated.

RESULTS

Bacteriological. Tobramycin disk sensitivity tests (10- μ g disks) were obtained on all 64 isolates reported here; MIC and MBC for tobramycin and gentamicin were determined for 57 of the isolates (Table 1). Zones of inhibition ranged from 14 to 24 mm with a median of 19, a mode of 20, and a mean of 18.8.

The MIC of tobramycin ranged from less than 0.05 to 1.5 μ g/ml with an MBC range from less than 0.05 to 3.1. Corresponding gentamicin MIC and MBC ranges were 0.05 to 6.2 and 0.1 to 12.5, respectively. The geometric mean MIC of tobramycin was 0.19 μ g/ml, whereas the corresponding value for gentamicin was 0.49.

Eighty-three percent of the strains showed zones of inhibition with tobramycin of 16 mm or greater, which has been recommended recently as a better critical diameter for prediction of susceptibility, as compared to the 14-mm size

TABLE 1. Comparison of susceptibility tests on 64 isolates of *P. aeruginosa*

Patient no.	Zone ^a diameter (mm)	Tobramycin (μ g/ml)		Gentamicin (μ g/ml)	
		MIC	MBC	MIC	MBC
1	23				
2A	20				
	21	0.1	0.4	0.2	0.2
2B	21	<0.05	<0.05	0.05	0.2
	23	0.1	0.2	0.2	0.4
3	20				
4	23	<0.2	<0.2	<0.2	<0.2
5	20	0.4	0.4	1.6	3.1
6	21	0.2	0.2	0.2	0.4
	20	0.1	0.8	0.4	0.4
	20	0.2	0.2	0.4	0.8
7	24	0.4	0.4	0.2	0.2
	19	0.1	0.2	0.1	0.1
8	18	0.4	0.8	3.1	6.2
	18	0.8	1.6	6.2	12.5
9A	18	0.4	0.8	0.8	1.6
	15	0.8	0.8	1.6	1.6
9B	16	0.1	0.2	0.4	0.4
	16	0.4	0.8	0.8	0.8
9C	14	0.2	0.4	0.8	1.6
	15	0.8	1.6	3.1	6.3
10	20	0.1	0.1	0.2	0.4
	23	0.05	0.2	0.2	0.2
11	19	<0.2	<0.2	0.4	0.4
	14	<0.2	<0.2	0.4	0.8
	17	<0.2	<0.2	0.8	0.8
12	23	0.05	0.2	0.4	0.8
	19	0.1	0.2	0.4	0.8
	22	0.1	0.2	0.8	0.8
	19	0.05	0.2	0.4	1.6
13	22	0.1	0.4	0.4	0.8
14	21	0.4	0.8	0.8	0.8
	18	0.1	0.2	0.8	1.6
	19	0.4	0.4	0.8	1.6
15	24				
	22	0.2	0.4	0.4	0.8
	20	0.2	0.4	0.05	0.1
	20	0.2	0.4	0.8	1.6
16	19	<0.2	0.4	<0.2	<0.2
	18	<0.2	<0.2	0.8	0.8
17A	18	0.4	0.4	0.8	1.6
	20	0.2	0.4	0.2	0.4
17B	14	0.8	0.8	3.1	3.1
	14	1.6	1.6	3.1	3.1
	14	0.4	0.4	1.6	1.6
	15	0.4	0.4	0.8	0.8
18	18	0.4	1.6	0.4	0.8
	20	0.4	0.8	0.4	0.8
	22	0.1	0.2	0.2	0.4
19	16				
20	15				
	14	1.6	3.1	3.1	6.2
	20	0.1	0.1	0.4	0.8
21	16	0.05	0.1	0.2	0.2
	18	0.2	0.1	0.2	0.4
	18	0.2	0.4	0.4	0.4
22	18	0.4	0.4	1.6	1.6
	21	<0.2	<0.2	<0.2	<0.2
23	15				
24	18	0.1	0.2	0.4	1.6
	18	0.4	0.4	1.6	1.6
	16	0.4	0.4	0.8	3.1
	20	0.4	0.4	0.8	1.6
25	20	0.1	0.2	0.2	0.4

^a Ten-microgram tobramycin disk.

used earlier (13, 14, 16). The 11 (17%) strains of *Pseudomonas* with zones of inhibition between 14 and 16 mm were isolated from five patients (no. 9, 11, 17, 20, 23), all of whom had clinically unsatisfactory responses. For these isolates, the mean MIC and MBC were 0.7 and 2.0 $\mu\text{g/ml}$.

For 80% (46/57) of the strains, the tobramycin MIC was less than the gentamicin MIC: seven strains showed differences of three tube dilutions; 20 showed two tube dilution differences; and 19 showed a one tube dilution difference. For eight strains the MIC with both antibiotics were identical, and only three strains were more susceptible to gentamicin (5.3%).

Similarly, 74% of the gentamicin MBC were greater than the corresponding tobramycin MBC (42/57: 12, three tube; 17, two tube; 13, one tube). For eight strains the MBC of both antibiotics was the same, whereas for seven strains gentamicin had a lower MBC. The correlation between tobramycin and gentamicin MIC and MBC is shown in Fig. 1 and 2, which demonstrate the significant difference in favor of tobramycin.

All *Pseudomonas* strains had an MIC of 1.6 $\mu\text{g/ml}$ or less with tobramycin, whereas 10.5% of the strains had an MIC greater than 1.6 $\mu\text{g/ml}$ with gentamicin.

Pharmacokinetics. Serum samples were obtained from 20 of the 25 patients, 13 of whom received tobramycin intramuscularly. After intramuscular injection (1.14 ± 0.22 mg/kg; mean $\pm$ standard deviation) the peak mean serum level obtained (at 1 h) was 4.81 ± 2.17 $\mu\text{g/ml}$ with 2-, 4- and 8-h levels of 3.24 ± 1.43 , 2.35 ± 1.30 , and 1.40 ± 1.09 (Fig. 3). Assay of serum

FIG. 1. Comparison of tobramycin and gentamicin MIC. The line of equal antipseudomonas activity is shown.

FIG. 2. Comparison of tobramycin and gentamicin MBC. The line of equal antipseudomonas activity is shown.

FIG. 3. Serum concentrations of tobramycin at various intervals after intramuscular injections of 1 to 1.6 mg/kg of body weight. n = number of sampling points. All values are the mean $\pm$ 1 standard deviation.

tobramycin levels from patients receiving the drug intravenously was precluded in our bioassay because of the concomitant administration of antibiotics such as clindamycin, tetracycline, or chloramphenicol.

After intramuscular injection of 1.1 mg/kg, serum tobramycin disappearance half-times of 33.0, 33.5, and 50.0 h were found in an azotemic patient (no. 6) who was undergoing intermittent hemodialysis for post-traumatic acute tubular necrosis. Doses of 1.3 mg/kg gave peak serum levels of 12 to 13 $\mu\text{g/ml}$ in this patient; 8.5 $\mu\text{g/ml}$ peaks were seen with 1.1 mg/kg.

Clinical results. Twenty-five patients, 10 females and 15 males, ranging in age from 17 to

78 years, were treated with tobramycin for serious *P. aeruginosa* infections (Table 2). The satisfactory clinical response rate for the 29 courses of therapy was 52% (15/29). Seven of the 16 courses of therapy in critically ill patients (44%) yielded satisfactory results. This compares with 50% of the seriously ill group (eight courses), and 80% of the moderately ill (five courses).

The results may also be examined by classifying the courses of treatment by disease entity (Table 2), or by antibiotic treatment (Table 3): group 1, tobramycin alone; group 2, tobramycin plus another antibiotic(s) not usually effective against *P. aeruginosa*; group 3, tobramycin plus another antibiotic(s), including carbenicillin in all instances. Group 2 contained cephalixin monohydrate, sodium cephalothin, chloramphenicol sodium succinate, clindamycin phosphate, ethambutol hydrochloride, isoniazid, potassium penicillin G, and tetracycline hydrochloride. Group 3 contained amphotericin B, disodium carbenicillin, sodium cephalothin, clindamycin phosphate, sodium methicillin, and tetracycline hydrochloride. Data on the susceptibility of the *P. aeruginosa* strains to these antibiotics were not available, with the exception that all strains from patients in group 3 were susceptible to carbenicillin. As indicated in Table 3, group 1 included six courses of therapy; group 2, nine; and group 3, 14. One-half of group 1 patients were moderately ill, whereas the majority of group 2 and 3 patients were seriously or critically ill (79%; 100%). All groups received essentially the same mean tobramycin dosage, though the mean and median duration of therapy were longer for group 3. Eighty-three percent of the patients receiving tobramycin alone responded satisfactorily, compared to 57% of those given tobramycin and carbenicillin and only 22% of those in group 2.

Two patients (no. 1, 2) with *Pseudomonas* bone and/or cartilage infections were treated successfully. Patient 1 (vertebral osteomyelitis) responded satisfactorily to a 56-day course of tobramycin alone, whereas the addition of carbenicillin and resection of the infected tissue was necessary before patient 2 (osteomyelitis and costochondritis) became culture negative.

Seven patients (no. 3 to 9) received tobramycin for infection of the urinary tract. The results were satisfactory except for patients 8 and 9. The former inadvertently received only two doses; the latter (patient 9) had received a renal transplant, still had her original kidneys, and was rejecting the transplant.

Two patients were treated for wound infec-

tion (no. 10, 11); one improved clinically and bacteriologically while on treatment; the other was very debilitated and eventually required re-operation for deep abdominal abscesses.

Six patients (including two with urinary tract infections) received tobramycin for respiratory tract infections (no. 6, 7, 12 to 15). Two of these patients failed to improve clinically, one (no. 14) died after receiving only 4 days of therapy while the other (no. 15), comatose and requiring continuous mechanical respiratory assistance, showed no clinical improvement on antimicrobial therapy.

Nine patients were treated for 10 episodes of pseudomonas septicemia, usually following severe thermal burns. Although maintenance of life and suppression of infection could be considered satisfactory in these patients, by our previously stated criteria of response, four of the episodes were considered to respond satisfactorily and six (60%) were unsatisfactory (one patient had one satisfactory and one unsatisfactory course of therapy). Four of five burn-associated septicemic patients who were therapeutic failures received tobramycin for 5 days or less; all five were in critical condition when tobramycin therapy was initiated.

Of 15 patients who had previously failed to improve with gentamicin alone (6 patients) or with carbenicillin (9 patients), six (40%) responded satisfactorily to tobramycin, either alone (2 patients) or with carbenicillin (4 patients). All four of the successful tobramycin-carbenicillin treatment courses followed previously unsuccessful gentamicin-carbenicillin therapy.

No clinical evidence of toxicity was detected in the 25 patients and laboratory evidence of toxicity was noted in only 4 of 24 patients studied. These four were critically ill septicemic patients (no. 21 to 23, 25) who had an average rise of serum creatinine of 1.5 mg/100 ml terminally; all were hypotensive, were receiving multiple other medications, and had received tobramycin for only 1 to 3 days.

Despite prolonged courses of tobramycin (11 courses longer than 2 weeks; four courses longer than 7 weeks), no ototoxicity was found either clinically or by serial audiography.

DISCUSSION

Tobramycin has been shown to be effective in the treatment of urinary tract infection, septicemia, and pneumonia due to various gram-negative bacilli (8, 9, 18). The evaluation of tobramycin in patients with *P. aeruginosa*

TABLE 2. Clinical diagnosis of *P. aeruginosa* infections and response to therapy with tobramycin

Patient no.	Age	Sex	Clinical diagnosis	Site of <i>Pseudomonas</i> culture	Tobramycin therapy (days)	Response to therapy ^a		Other significant bacterial isolates (other antibiotics) ^a
						Clinical	Bacteriological	
1	47	M	Osteomyelitis of vertebrae	Aspirate of disk	56	S	ND	(I, E)
2A	56	M	Osteomyelitis and costochondritis of ribs	Wound	31	S	US	(Ca)
2B	56	M	Osteomyelitis and costochondritis of ribs	Pleural fluid				
				Wound	53	S	S	(Ca)
				Cartilage				
3	29	M	Urinary tract infection; closed head trauma	Urine	10	S	S	Urine: <i>S. faecalis</i>
4	41	F	Urinary tract infection; nephrostomy; Stage III carcinoma of uterine cervix	Urine	9	S	S	<i>E. cloacae</i>
5	44	F	Pyelonephritis; ureteral diversion; flaccid paralysis-polio	Urine	10	S	S	Urine: <i>K. pneumoniae</i>
6	23	M	Urinary tract infection; acute tubular necrosis; pneumonitis; closed head trauma	Urine	14	S	US	Urine: <i>E. aerogenes</i> (P)
				Sputum				
7	62	F	Urinary tract infection; pneumonia; scleroderma; obstruction of left bronchus	Sputum	11	S	ND	Sputum: <i>K. pneumoniae</i>
				Urine				<i>Serratia</i>
8	45	M	Bacteriuria; renal transplant	Urine	1	US	ND	<i>E. coli</i> (Ca)
9A	33	F	Urinary tract infection; renal transplant	Urine	9	US	US	(I)
9B	33	F	Persistent bacteriuria	Urine	6	US	US	Urine: <i>E. coli</i> (Ce, Ch)
								Urine: <i>B. fragilis</i>
								<i>S. faecalis</i>
9C	33	F	Persistent bacteriuria	Urine	6	US	US	Urine: <i>S. faecalis</i>
								<i>E. coli</i> (Ce, Ch, Cy)
10	78	M	Wound infection, surgical	Wound	14	S	S	Wound: <i>S. faecalis</i>
				Sputum				Sputum: <i>K. pneumoniae</i>
11	43	F	Wound infection; peritonitis; colectomy	Wound	13	US	US	<i>E. cloacae</i>
								Wound: <i>S. faecalis</i>
								<i>P. morganii</i>
12	49	F	Pneumonia; myasthenia gravis; thymectomy	Sputum	36	S	S	<i>E. cloacae</i> (Ch)

13	26	M	Pneumonia; chronic obstructive pulmonary disease	Sputum	24	S	S	Sputum: <i>S. aureus</i> <i>K. pneumoniae</i> <i>Serratia</i> (Ca, Cy) (Ca, Cy)
14	28	M	Pneumonia; mediastinitis; colonic transposition with anastomatic leak	Sputum	4	S	S	
15	65	F	Pneumonia; subarachnoid hemorrhage, coma	Sputum	10	S	S	Sputum: <i>S. faecalis</i> <i>P. stuartii</i> <i>K. pneumoniae</i> (Ca)
16	17	M	Septicemia; 84% burns	Blood	23	S	US	Blood: <i>P. mirabilis</i> <i>E. coli</i> (Ca, M, T)
17A	28	M	Septicemia; 72% burns	Blood Sputum	34	S	US	Blood: <i>P. stuartii</i> Sputum: <i>E. coli</i> <i>K. pneumoniae</i> (A, Ca)
17B	28	M	Septicemia; 72% burns	Blood Sputum Cornea Scrotal abscess	10	US	US	Blood: <i>P. mirabilis</i> <i>Serratia</i> (Ca, Ch)
18	25	M	Septicemia; 50% burns	Blood	13	S	US	Blood: <i>S. faecalis</i> <i>E. cloacae</i> (Ca)
19	17	M	Septicemia; 80% burns	Sputum Blood Wound	64	S	US	Sputum: <i>K. pneumoniae</i> <i>P. mirabilis</i> Wound: <i>S. faecalis</i> (A, Ca) Blood: <i>P. stuartii</i> (T)
20	20	M	Septicemia; 66% burns	Blood	5	US	US	
21	42	F	Septicemia; 67% burns	Sputum Blood Sputum	3	US	ND	Blood: <i>E. coli</i> <i>Serratia</i> (Cr, P)
22	46	M	Septicemia; 50% burns	Blood	2	US	ND	Blood: <i>P. mirabilis</i> (Ca)
23	27	M	Septicemia; 80% burns	Blood	1	US	ND	Blood: <i>S. faecalis</i> (Ca)
24	24	F	Septicemia; peritonitis; abdominal abscess; ulcerative colitis	Peritoneal fluid Wound Sputum Urine	83	US	US	Peritoneal fluid: <i>E. coli</i> (A, Ca, Cy)
25	48	F	Subphrenic abscess	Abscess	1	US	ND	Abscess: <i>E. aerogenes</i> <i>S. faecalis</i> (Cr)

^a S, Satisfactory; US, unsatisfactory; ND, not done.

^b A, Amphoteracin B; Ca, disodium carbenicillin; Ce, cephalixin monohydrate; Ch, sodium cephalothin; Cr, chloramphenicol sodium succinate; Cy, clindamycin phosphate; E, ethambutol hydrochloride; I, isoniazid; M, sodium methicillin; P, potassium penicillin G; T, tetracycline hydrochloride.

TABLE 3. Summary of 29 courses of therapy in relation to antibiotics administered

Determination	Group		
	I ^a	II ^b	III ^c
No. of courses of therapy	6	9	14
Clinical condition (%)			
Moderately ill	50	22	0
Seriously ill	17	44	29
Critically ill	33	33	71
Tobramycin dose (mean, mg/kg/day)	3.5	3.8	3.9
Duration of therapy (days)			
Mean	14	12	26
Median	10	6	18
Satisfactory response (%)	83	22	57

^a Tobramycin alone.

^b Tobramycin with other antibiotics not usually active against *P. aeruginosa*.

^c Tobramycin with other antibiotics, including carbenicillin in all cases.

infection is appropriate because of the in vitro advantages of this aminoglycoside over gentamicin. The patients receiving tobramycin in this study were seriously ill with 80% considered initially in serious or critical condition. All 25 patients were infected with *P. aeruginosa*; 19 had polymicrobial infections and received other antibiotics concomitantly. The overall satisfactory response rate of 52% in the present series compares favorably with published results of *P. aeruginosa* infections treated with tobramycin: Klastersky et al. (9), 42%; Westenfelder et al. (18), 67%. The former series included both cases of urinary tract infection (14 cases) and systemic infection (17 cases); the latter reported only urinary tract infections (17 cases).

As would be expected, patients with urinary tract infections responded well to tobramycin, with five of seven patients showing a satisfactory response. Two of these five had pneumonitis as well. One of the two treatment failures received only one dose of tobramycin; the other was a transplant patient whose bacteriuria could not be eradicated, possibly because of retention of nonfunctioning infected kidneys.

The two patients with serious bone or cartilage infections also responded very well to prolonged therapy, although one patient required excision of the infected tissue followed by a second course of therapy. The degree of accumulation of tobramycin in bone or cartilage has not been reported.

As a group, patients receiving tobramycin alone were least ill and had the highest satisfactory response rate. The seriously and critically ill patients usually received multiple antibiotics, and those who received a second anti-

pseudomonas drug (carbenicillin; group 3) were more likely to have a satisfactory outcome. Because drug dosage differed little among the three groups, the differences observed in satisfactory response rates can not be explained by this factor. The poorest prognosis was associated with those seriously and critically ill patients receiving only one anti-pseudomonas drug (tobramycin; group 2).

We found no direct correlation between peak tobramycin serum levels and clinical response. The mean serum concentration of tobramycin 8 h after dosing (1.40 µg/ml) was well above the mean MIC for the strains of *Pseudomonas* tested (0.19 µg/ml). The mean tobramycin serum levels we noted 2 and 8 h after intramuscular injection (4.81 and 1.40 µg/ml) are similar to those noted by Jaffe et al. (5.1 and 1.9 µg/ml) (8).

While all the aminoglycosides (including tobramycin) are nephro- and ototoxic, we did not observe either adverse effect in this small series of patients, despite obtaining serial serum creatinine determinations and audiography in patients whose clinical conditions permitted it (4, 10). Most gentamicin toxicity has been associated with serum levels of 8 to 12 µg/ml or higher (5, 17). Since the pharmacokinetics and toxic characteristics of gentamicin and tobramycin are nearly alike, comparable serum levels of tobramycin might be expected to be toxic (15). Tobramycin serum levels greater than 9.0 µg/ml were found only three times after intramuscular administration of the antibiotic. In one case, high serum levels (12.0, 13.5 µg/ml) were initially obtained in an azotemic patient (no. 6); adjustment of dosage brought serum levels below 8 µg/ml.

The other two high serum concentrations (9.1 and 9.2 µg/ml) occurred in patients 1 and 17 and were isolated events, possibly reflecting either variable absorption from the injection site, or variability intrinsic in the assay method. These data suggest that maintenance of serum levels below the 8- to 12-µg/ml level is associated with a low incidence of toxicity. One can only speculate, however, whether a higher success rate could be achieved by maintaining higher (and more toxic) serum levels.

We conclude that tobramycin can safely be used to treat serious *P. aeruginosa* infections. Treatment of seriously or critically ill patients was most successful when carbenicillin was used in conjunction with tobramycin. Although comparable data for gentamicin-treated tobramycin-failures are lacking, it should be noted that four of nine patients (44%) who previously received gentamicin and carbenicillin without improvement did respond satisfactorily to to-

bramycin and carbenicillin therapy. Our data confirm the previously reported lower tobramycin MIC for *Pseudomonas*. The lower success in the 10 episodes of septicemia suggest that dosages of tobramycin possibly should be increased above those used in this study for life-threatening infections.

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