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Pharmacokinetic Studies of Tobramycin and Gentamicin

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Broth dilution susceptibility tests of 100 isolates of *Pseudomonas aeruginosa* and 101 isolates of *Staphylococcus aureus* against tobramycin (formerly nebramycin factor 6) and gentamicin showed that tobramycin was more effective against *P. aeruginosa* and less effective against *S. aureus*. The minimal inhibitory concentration of tobramycin against the *Pseudomonas* sp. isolates that required 5 μg of gentamicin per ml for inhibition ranged from 0.63 to 0.31 μg/ml. Peak concentrations in the blood of 10 healthy adults after intramuscular injection of 80 and 40 mg of tobramycin averaged 3.7 ± 0.62 and 2.4 ± 0.27 μg/ml, and declined to 0.56 ± 0.05 and 0.26 ± 0.02 μg/ml, respectively, after 6 h. The urine recovery averaged 60%. The half-life was 1.6 h. During continuous intravenous infusion of tobramycin and gentamicin (infusion rate 6.6 mg per h), blood levels at steady state were 0.94 ± 0.10 and 1.04 ± 0.06 μg/ml, respectively. For both antibiotics, the calculated distribution volume ranged from 15 to 17 liters. The renal clearance of tobramycin averaged 76% and that of gentamicin averaged 85% of the total clearance, indicating that the drugs are primarily eliminated by the kidneys. The present results suggest that tobramycin may be more successful in the treatment of *Pseudomonas* infections than gentamicin at the same dosage (80 mg intramuscularly three to four times daily).

Nebramycin, an antibiotic complex of at least seven factors, was first described in 1967 by Stark et al. (20). Nebramycin belongs to the aminoglycosidic family of antibiotics, which includes kanamycin, neomycin, gentamicin, and paromomycin. The antibiotic complex is produced by fermentation biosynthesis with the use of *Streptomyces tenebrarius* (11). Chromatographic studies have shown that the complex consists of factors 1, 1', 2, 3, 4, 5, and 6 (22). Factors 1, 1', and 3 are found only in small amounts and are, therefore, not significant. Of special interest was factor 6 of the nebramycin complex (tobramycin), because it had a favorable antibacterial spectrum and the best in vitro activity of any of the factors. The toxicity of tobramycin is slightly greater than that of the complex and of factor 2. Wick and Welles (25) compared the nephrotoxicity of tobramycin and gentamicin in rats and found that tobramycin was less nephrotoxic than gentamicin (evidenced by urine glutamic oxalacetic transaminase concentrations, renal tubular cell excretion, and histopathological examination of renal tissue). As with other aminoglycoside antibiotics, ototoxic side effects (especially vestibular damage) were produced by higher doses in animal studies. Overall, it appears that the toxicity of tobramycin is similar to that of kanamycin and less than that of neomycin B and gentamicin.

Tobramycin, which had been isolated from the nebramycin complex, was made available in purified form. The molecular formula of tobramycin is $C_{18}H_{37}N_5O_9 \cdot 3H_2O$ (14). The antibiotic is a colorless, hygroscopic substance which is very soluble in water. The crystalline form is available as mono-, di-, or trihydrate. The chemical behavior of tobramycin is similar to that of other aminoglycoside antibiotics. Splitting of tobramycin by 6 N HCl yields 3-amino-3-deoxy-D-glucose and nebramine, a $C_{12}H_{26}N_4O_5$ compound. Both solution and crystalline tobramycin are very stable at room temperature and 37 C between pH 3 and 11. Solutions can be autoclaved for 20 min with no loss of potency (22).

The antibacterial spectrum of tobramycin is similar to that of gentamicin, including activity against staphylococci and most gram-negative bacteria. It is weakly active against streptococci and pneumococci. The in vitro activity

of tobramycin is quite similar to that of gentamicin against most bacteria, including staphylococci; however, its activity against *Pseudomonas aeruginosa* is definitely higher (2). This was observed not only with gentamicin-susceptible isolates of *Pseudomonas*, for which susceptibility differs by 1 to 3 geometric $\log_2$ dilutions in the test, but also with cultures that are completely resistant or only slightly susceptible to gentamicin. The in vitro minimal inhibitory concentration (MIC) determinations are adversely affected to a large extent by increased salt concentrations of media. For example, the MIC of tobramycin against the culture of *Staphylococcus aureus* 3055 tested (25) was 0.15 μg/ml in a NaCl-free medium whereas it was 2.5 μg/ml in a medium containing 1% NaCl. These studies show that reports on MIC values, especially for tobramycin and gentamicin, must always include a description of the method and medium employed. Preston and Wick (17) found that the test results are also affected by the agar content; thus, inhibitory concentrations of tobramycin are far lower in nutrient broth than in an agar-containing medium.

Black and Griffith (2) reported on serum levels after intramuscular injection of tobramycin and showed that, independently of the dosage, peak concentrations in serum were achieved in 30 min. Also, after the administration of 25, 50, and 75 mg, mean serum concentrations of tobramycin were 0.26, 0.56, and 0.90 μg/ml, respectively, after 4 h (concentrations were proportionate to the dose). When comparing the serum levels of gentamicin and tobramycin after intramuscular injection of corresponding doses, these same authors found that gentamicin serum concentrations were not significantly higher than those for tobramycin. An average of 38.3% of administered antibiotic was found in urine after intramuscular injection of 75 mg of tobramycin. Accordingly, these investigators concluded that there was no significant difference in the calculated elimination constants and distribution coefficients of tobramycin and gentamicin.

The purpose of this paper is to compare the antibacterial activity of tobramycin with that of gentamicin, especially against *P. aeruginosa* and *S. aureus*. Determinations were also made of the pharmacokinetic constants of tobramycin (elimination constants, area under the blood level curve, and distribution volume) to assess the properties of this new antibiotic. From the serum levels obtained and the half-life calculated, recommendations might be made for an optimal dosage of tobramycin for intramuscular injection and for continuous intravenous infusion.

MATERIALS AND METHODS

Bacteria. Cultures of *P. aeruginosa* (100 isolates) and *S. aureus* (101 isolates) tested in this study were obtained from clinical specimens at the Pediatric University Clinic, Kiel, Germany.

MIC determinations. For MIC determinations, all isolates of *Pseudomonas* sp. and *Staphylococcus* sp. were incubated overnight in nutrient broth at 37 C. On the next day, tubes containing decreasing concentrations in $\log_2$ dilutions of tobramycin or gentamicin (20 to 0.04 μg/ml) in a liquid medium (Antibiotic Medium 3, Difco; Penassay broth) were inoculated with 0.1 ml of a 1:100 dilution from each culture. After incubation for 18 h at 37 C, the MIC was read as the lowest concentration of antibiotic inhibiting visible growth.

Human volunteers. Subjects used in the 33 blood level studies of tobramycin and gentamicin were 18 healthy males, 21 to 43 years old, weighing 65 to 90 kg. None of the volunteers had received any prior medication.

Procedure for obtaining serum or urine specimens. Tobramycin (Eli Lilly & Co.) and gentamicin (Refobacin; Merck, Darmstadt, Germany) were available in ampoule form. Ampoules of tobramycin contained 50 mg of base per ml; ampoules of gentamicin contained 40 mg. Administration consisted of a single intramuscular injection of varied doses of tobramycin, or continuous infusion over 4 h with the infusion rate at 6.6 mg per h in 6 ml of solution. Solutions of tobramycin and gentamicin were diluted in infusion solution, Tutofusin NS (Pfrimmer). Uniformity of the infusion rate was assured by use of an adjustable perfusor (Braun, Melsungen). At the end of the infusion period, a previously calculated rest volume was left in the perfusor. After intramuscular administration, blood was withdrawn at 15-min intervals during the first hour, at 30-min intervals until the sixth hour, and after 8 and 12 h. During continuous intravenous infusion, blood samples were taken at 15-min intervals during the first hour, at 30-min intervals until the fourth hour, after termination of the infusion at 15, 30, and 60 min, and then at intervals of 30 min until the seventh hour.

After intramuscular administration, urine was collected over 3-h periods until the twelfth hour, the volume was recorded, and the antibiotic concentration in each portion was determined. The amount of antibiotic excreted was calculated from the volume and the concentration. During continuous intravenous infusion, portions of urine were collected during the first 3 h, during the fourth hour, and during the fifth to seventh hours.

Microbiological assay. The concentrations of tobramycin and gentamicin were determined by the agar diffusion method with *Bacillus subtilis* (ATCC 6633) as test organism and Difco Antibiotic Medium

5 as medium. The holes punched into the agar (7 mm in diameter) were filled with 0.05 ml of serum or standard solution diluted in normal pooled serum. Urine specimens were diluted 1:10 in pH 8.0 phosphate buffer. For urine assay, the standard solutions were also prepared in pH 8.0 buffer. From 12 individual standard curves representing the relation between zone diameters and falling concentrations of tobramycin and gentamicin, a mean standard curve was obtained by regression, which was taken as the basis for the evaluation of zone diameters of serum and diluted urine samples. To correct methodological errors which are explainable by slight variations in the agar depth, seeding density, etc., four samples of previously prepared reference standard of the same concentration of 2.5 μg/ml were pipetted into punched holes on each agar plate. If the average zone diameters of the four standard samples deviated from the previously plotted mean value, all zone diameters of the corresponding plate were corrected.

Calculation of pharmacokinetic constants. The determination of the pharmacokinetic constants for intravenous administration was based on the model developed by Gehler and Kübler (9a). The calculation process works according to the method of least squares and had previously been employed successfully in other studies.

The usual pharmacokinetic models for the calculation of blood level curves are not suitable when a drug has not been completely absorbed after oral administration. Therefore, calculations were first made by means of regression analysis for approximate k_2 (elimination constant) from the declining segment of the curve measured for each person; then the absorption curve, according to Gehler and Kübler (9a), was reconstructed, and the value for y_0 (initial concentration) was determined. According to Gehler and Kübler, the absorbed dose (in percent) is derived from the ratio between y_0 after oral administration and y_0 after intravenous administration. The pharmacokinetic constants representative for each test group were obtained by averaging the individual constants.

RESULTS

In vitro activity. Of the 100 cultures of *P. aeruginosa*, 85% of the isolates were inhibited by gentamicin concentrations of 1.25 to 2.5 μg/ml (Fig. 1, Table 1); the MIC of tobramycin ranged from 0.63 to 1.25 μg/ml for 81% of the isolates. Only 5% of the isolates were more susceptible to gentamicin than to tobramycin. The percentage of cultures with a higher susceptibility to tobramycin was 19%. In general, the MICs of tobramycin were lower by 1 to 2 $\log_2$ geometric dilution series. Ten percent of the *Pseudomonas* cultures that required 5 μg of gentamicin per ml for inhibition were more susceptible to tobramycin by 3 to 4 geometric dilutions (range of MICs, 0.63 to 0.31 μg/ml).

Of the 101 cultures of *S. aureus* tested (Fig. 2, Table 1), 70% were inhibited by tobramycin at concentrations in the range of 0.31 to 1.25 μg/ml, whereas 67% of the isolates were inhibited by gentamicin at a MIC of 0.31 μg/ml. The relatively wide range in the in vitro susceptibility of *S. aureus* to tobramycin is striking. Sixteen percent of the isolates of staphylococcus that required concentrations of 2.5 μg of tobramycin per ml for inhibition were more susceptible, by the method used, to gentamicin by 2 to 3 geometric dilutions.

The in vitro susceptibility tests for a larger number of cultures of pseudomonads and staphylococci demonstrate that tobramycin is definitely more effective than gentamicin against *P. aeruginosa*, whereas gentamicin appears more active, in vitro, against *S. aureus*.

Pharmacokinetics. After intramuscular in-

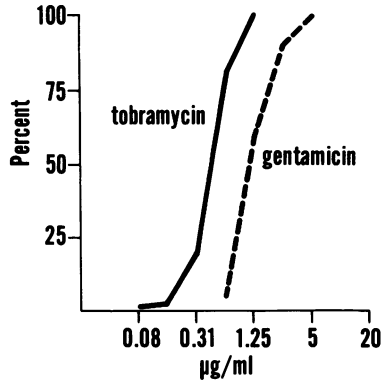

FIG. 1. *Cumulative percentage of 100 isolates of Pseudomonas aeruginosa inhibited by various concentrations of tobramycin and gentamicin.*

TABLE 1. *Percentage of 100 Pseudomonas isolates and 101 Staphylococcus isolates inhibited by tobramycin and gentamicin as determined by a broth dilution method*

Minimal inhibiting concn (μg/ml)	*Pseudomonas* isolates inhibited by		Staphylococcal isolates inhibited by	
	Tobramycin (%)	Gentamicin (%)	Tobramycin (%)	Gentamicin (%)
20				
10				
5		10		
2.5		32	16	
1.25	20	53	36	
0.63	61	5	25	22
0.31	17		9	67
0.16	1		4	11
0.08	1		4	
0.04			6	

jections of 40 to 80 mg of tobramycin, peak serum concentrations were obtained after 30 min (average, 2.4 μg/ml after 40 mg and 3.7 μg/ml after 80 mg), as is shown in Table 2 and Fig. 3. Calculating t_{max} (time of maximal blood level) on the basis of the Bateman function, the value was 0.78 h for the dosage of 40 mg and 0.67 h for the dosage of 80 mg (no significant difference). At 6 h after intramuscular administration, serum levels averaged 0.26 μg/ml (after 40 mg) and 0.56 μg/ml (after 80 mg). The drug content of the serum had declined to nonmeasurable concentrations of 0.1 μg/ml at approximately 8 and 12 h, respectively, for the 40- and 80-mg dosages (Fig. 3).

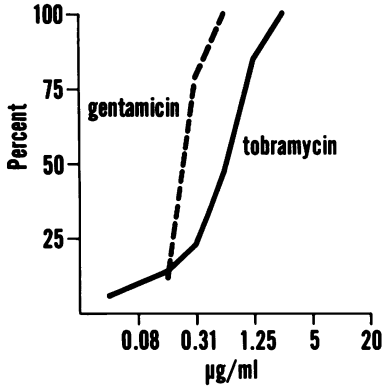

FIG. 2. *Cumulative percentage of 101 isolates of Staphylococcus aureus inhibited by various concentrations of tobramycin and gentamicin.*

TABLE 2. *Mean concentrations of tobramycin in the serum of healthy adults after parenteral administration of 80 and 40 mg as an intramuscular injection (10 persons) and of 6.6 mg per h as a continuous intravenous infusion (6 persons)*

Time (h) after application	Mean serum levels (μg/ml) after		
	80 mg	40 mg	Continuous infusion
0.25	2.69 ± 0.28	2.15 ± 0.28	0.31 ± 0.06
0.5	3.67 ± 0.26	2.41 ± 0.27	0.40 ± 0.05
0.75	3.54 ± 0.23	2.33 ± 0.32	0.63 ± 0.12
1	3.32 ± 0.27	2.16 ± 0.24	0.82 ± 0.10
1.5	2.46 ± 0.21	1.60 ± 0.13	0.86 ± 0.10
2	2.10 ± 0.14	1.27 ± 0.13	0.92 ± 0.10
2.5	1.89 ± 0.16	1.07 ± 0.10	1.06 ± 0.16
3	1.50 ± 0.10	0.85 ± 0.07	1.05 ± 0.17
3.5	1.32 ± 0.08	0.75 ± 0.06	0.93 ± 0.09
4	1.18 ± 0.07	0.65 ± 0.05	0.88 ± 0.09
4.25			0.78 ± 0.09
4.5	0.97 ± 0.05	0.55 ± 0.03	0.66 ± 0.08
5	0.82 ± 0.05	0.48 ± 0.02	0.58 ± 0.07
5.5	0.68 ± 0.05	0.36 ± 0.02	0.47 ± 0.04
6	0.56 ± 0.05	0.26 ± 0.02	0.39 ± 0.05
6.5			0.30 ± 0.03
7			0.23 ± 0.04
8	0.28 ± 0.02	0.13 ± 0.01	
12	0.10 ± 0.01		

In accordance with the rapid absorption, mathematic calculation yielded a relatively high absorption constant of 4.0 to 4.9 (Table 3) and, as can be expected from the relatively rapid decline of the serum concentration curve, an elimination constant of 0.43, which corresponded to a biological half-life of 1.6 h. The area under the blood concentration curve increased from an average of 6.8 to 11.9 h·μg/ml when the dosage was doubled, indicating that serum levels were proportionate to the dose.

The highest urine concentrations (Table 4) were achieved during the first 3 h (60 to 115 μg/ml after 40 mg and 90 to 500 μg/ml after 80 mg). During the second and third 3-h period, urine levels were considerably lower; however, they still exceeded the MIC values for the isolates of *Pseudomonas* and *Staphylococcus* tested. Between the 10th and 12th h, tobramycin was no longer demonstrable in the urine after the dosage of 40 mg, whereas urine

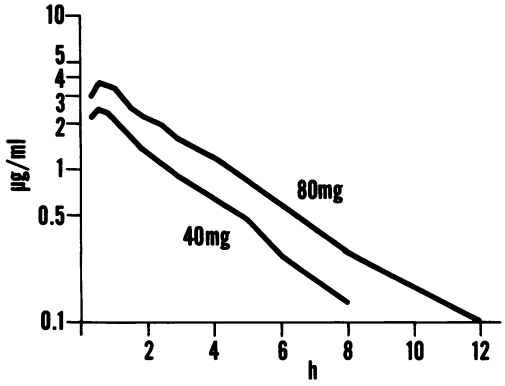

FIG. 3. *Mean tobramycin concentrations in the serum of 10 healthy adults after intramuscular injection of 40 and 80 mg.*

TABLE 3. *Pharmacokinetic constants of tobramycin after intramuscular injection of 80 and 40 mg in 10 healthy adults*

Pharmacokinetic constant[a]	Value after injection of	
	80 mg	40 mg
k_1	4.92 ± 1.32	4.02 ± 1.09
k_2	0.33 ± 0.01	0.43 ± 0.02
$t_{50\%}$ (h)	2.14 ± 0.06	1.63 ± 0.07
t_{max} (h)	0.67 ± 0.14	0.78 ± 0.16
F (h·μg/ml)	11.92 ± 0.64	6.77 ± 0.48

[a] k_1, Absorption constant; k_2, elimination constant; $t_{50\%}$, biological half-life; t_{max}, time until maximal serum level; F, area under the curve.

TABLE 4. *Urine concentrations and urine recovery after intramuscular injection of 80 and 40 mg of tobramycin in 10 healthy adults*

Dose (mg)	Urine concn (μg/ml)				Urine recovery (%)					
	0–3 h	4–6 h	7–9 h	10–12 h	0–3 h	4–6 h	7–9 h	10–12 h	0–9 h	0–12 h
80	90–500	20–90	9–36	8–28	42.7	10.3	5.3	2.3	58.3	60.6
40	60–115	16–54	3–23	—	40.2	16.3	6.1	—	62.6	—

concentrations ranged from 8 to 28 μg/ml after the 80-mg dose. The urine recovery by the 10th h averaged 62% after 40 mg and 58% after 80 mg.

When tobramycin was given by continuous intravenous infusion over 4 h at an infusion rate of 6.6 mg per h, peak serum concentrations were achieved at 2.5 to 3 h. Steady-state blood concentrations averaged 0.94 μg/ml (Fig. 4, Tables 2 and 5). As pharmacokinetic constants, an elimination constant of 0.43 (equivalent to that found after intramuscular injection), a biological half-life of 1.6 h, and a mean distribution volume of 16.9 liters were calculated (Table 5). The latter is somewhat higher than the body's average content of extracellular water (15 to 16% of body weight). The distribution coefficient (distribution volume divided by body weight) averaged 0.24. A value of 4.75 h·μg/ml was calculated as the area under the blood concentration curve.

When the same dosage of gentamicin was given by continuous intravenous infusion over 4 h (infusion rate, 6.6 mg/h), values corresponding to tobramycin were observed (Table 5). There was no significant difference when assuming a 1% error probability. During continuous infusion of gentamicin, the blood level, at steady state, averaged 1.04 μg/ml, the elimination constant was 0.41 (corresponding to a half-life of 1.7 h), and the area under the blood concentration curve was 5.19 h·μg/ml). The distribution volume was calculated to be 14.4 liters and thus somewhat lower than that of tobramycin, but the difference was not significant. The distribution coefficient was found to be 0.21.

From the clearance studies performed during continuous intravenous infusion of tobramycin and gentamicin, the total clearance of tobramycin averaged 115.7 ml/min, and the total clearance of gentamicin averaged 95.8 ml/min (no significant difference). The renal clearance was 87.9 ml/min for tobramycin and 81.8 ml/min for gentamicin (76 and 85% of total clearance). The resulting mean value of extrarenal clearance is 24% and 15%, respectively (difference not significant). The average urine recovery during the fourth hour after the beginning of the infusion was found to be 59.2% of tobramycin and 60.2% of gentamicin.

DISCUSSION

In accordance with the literature (2, 17, 25), the in vitro activity of tobramycin against 100

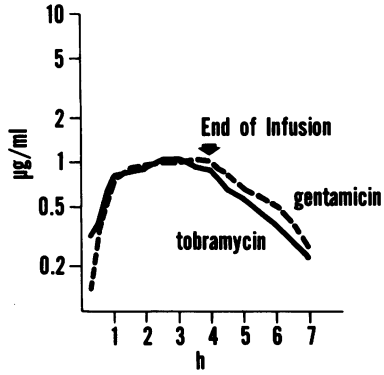

FIG. 4. *Mean serum concentrations for continuous infusion of tobramycin (in six persons) and of gentamicin (in seven persons) in the dosage of 6.6 mg per h.*

TABLE 5. *Pharmacokinetic constants (mean values) after continuous intravenous infusion of tobramycin (in six persons) and of gentamicin (in seven persons) in a dosage of 6.6 mg per h*

Determination	Tobramycin	Gentamicin
Serum level (μg/ml) at steady state	0.94 ± 0.10	1.04 ± 0.06
Distribution volume (liters)	16.90 ± 1.60	14.45 ± 1.70
Distribution coefficient	0.24 ± 0.02	0.21 ± 0.02
Elimination constant	0.43 ± 0.02	0.41 ± 0.03
Area under the curve (h·μg/ml)	4.75 ± 0.41	5.19 ± 0.20
Half-life (h)	1.59 ± 0.08	1.73 ± 0.14
Total clearance (ml/min)[a]	115.70 ± 9.50	95.80 ± 7.00
Renal clearance (ml/min)[a]	87.90 ± 9.50	81.80 ± 9.20
Urine concentrations (μg/ml)[b]	20–83	47–82
Urine recovery (%)[b]	59.2	60.2

[a] Related to 1.73 m² of body surface.
[b] Fourth hour after start of infusion.

isolates of *P. aeruginosa* was definitely better than that of gentamicin; this was particularly evident with isolates that are only slightly susceptible to gentamicin. The in vitro antibacterial activity of tobramycin was lower against the isolates of staphylococci tested, as has been reported by the same authors.

When the pharmacokinetics of both tobramycin and gentamicin after intravenous administration were compared, there were no significant differences evident regarding distribution and elimination. Likewise, the concentrations of antibiotic in serum achieved after intramuscular administration of tobramycin are quite consistent with those reported for gentamicin with similar dosage schedules (2, 13, 19, 24).

Tobramycin, which has potential toxicological characteristics very similar to those of gentamicin, can be expected to be effective in therapy of infections caused by susceptible organisms. In fact, tobramycin might be preferred for use in *Pseudomonas* infections. Since the therapeutic results with gentamicin in *Pseudomonas* infection in some cases have not been satisfactory (5, 9, 12, 16, 18, 21, 23), the in vitro susceptibility data showing that tobramycin has better antibacterial activity than gentamicin may mean that tobramycin, at the same dosage, could result in successful therapy. For gentamicin, a daily dosage of 2.4 to 3.2 mg per kg of body weight is recommended today by most authors (4, 8, 10). For adequate therapeutic effect, tobramycin should be administered to adults at a dosage of 80 mg three to four times daily.

LITERATURE CITED

1. Betzien, G., and W. Vömel. 1970. Pharmacokinetic studies of chloramphenicol, p. 914. *In* Progress in antimicrobial and anticancer chemotherapy. Proc. 6th Int. Congr. Chemother., vol. 2. University Tokyo Press, Tokyo.
2. Black, H. R., and R. S. Griffith. 1971. Preliminary studies with nebramycin factor 6. Antimicrob. Ag. Chemother. 1970, p. 314-321.
3. Bulger, R. J., S. Sidell, and W. M. M. Kirby. 1963. Laboratory and clinical studies of gentamicin. Ann. Intern. Med. **59**:593-604.
4. Cox, C. E. 1969. Gentamicin, a new aminoglycoside antibiotic: clinical and laboratory studies in urinary tract infection. J. Infect. Dis. **119**:486-491.
5. Darrell, J. H., and P. M. Waterworth. 1967. Dosage of gentamicin for Pseudomonas infections. Brit. Med. J. **2**:535-537.
6. Dost, F. H. 1968. Grundlagen der Pharmakokinetik, 2nd ed. Georg Thieme Verlag, Stuttgart.
7. Earle, D. P., and R. B. Berliner. 1946. Simplified clinical procedure for measurement of glomerular filtration rate and renal plasma flow. Proc. Soc. Exp. Biol. Med. **62**:262-264.
8. Federspil, P. 1969. Clinical use of gentamicin in ear, nose, and throat infections. J. Infect. Dis. **119**:465-470.
9. Garrod, L. P., and F. O'Grady. 1972. Antibiotic and chemotherapy, 3rd ed., p. 126-129. Churchill Livingstone, Edinburgh.

9a. Gehler, J., and W. Kuebler. 1970. Verteilungsstudien mit intravenös infundierter Askorbinsäure. Int. Z. Vitaminforsch. **40**:454-464.

10. Gingell, J. C., G. D. Chisholm, J. S. Calnan, and P. M. Waterworth. 1969. The dose, distribution, and excretion of gentamicin with special reference to renal failure. J. Infect. Dis. **119**:396-401.
11. Higgens, C. E., and R. E. Kastner. 1968. Nebramycin, a new broad-spectrum antibiotic complex. II. Description of *Streptomyces tenebrarius*. Antimicrob. Ag. Chemother. 1967, p. 324-331.
12. Holt, R. J., and R. L. Newman. 1968. Gentamicin in urinary infections of children. Arch. Dis. Childhood **43**:329-333.
13. Kobyletzki, D. v., H. Wahlit, and F. Gebhardt. 1969. Zur Pharmakokinetik von Gentamycin im Serum und Harn. Med. Klin. **34**:1497-1502.
14. Koch, K. F., and J. A. Rhoades. 1971. Structure of nebramycin factor 6, a new aminoglycosidic antibiotic. Antimicrob. Ag. Chemother. 1970, p. 309-313.
15. Krüger-Thiemer, E., and B. Schlender. 1963. Die Lösung chemotherapeutischer Probleme durch programmgesteuerte Ziffernrechenautomaten. 2. Die exakte Berechnung der Gleichungsparameter und ihrer Vertrauensgrenze mit Hilfe des Gauss-Newton-Iterationsverfahrens. Arzneim.-Forsch. **13**:891-894.
16. Nunnery, A. W., and Riley, H. D. 1969. Gentamicin: clinical and laboratory studies in infants and children. J. Infect. Dis. **119**:460-464.
17. 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.
18. Reutter, F. W., and H. Modde. 1969. Klinische Erfahrungen mit Gentamycin in der Behandlung von Harnwegsinfekten. Ther. Umsch. **1**:32-35.
19. Simon, C., and W. Stille. 1970. Antibiotika-Therapie in Klinik and Praxis, p. 69-71. F. K. Schattauer Verlag, Stuttgart.
20. Stark, W. M., M. M. Hoehn, and N. G. Knox. 1968. Nebramycin, a new broad-spectrum antibiotic complex. I. Detection and biosynthesis. Antimicrob. Ag. Chemother. 1967, p. 314-323.
21. Sweedler, D. R., C. F. Gravenkemper, R. J. Bulger, J. L. Brodie, and W. M. Kirby. 1964. Laboratory and clinical studies of gentamicin. Antimicrob. Ag. Chemother. 1963, p. 157-160.
22. Thompson, R. Q., and E. A. Presti. 1968. Nebramycin, a new broad-spectrum antibiotic complex. III. Isolation and chemical-physical properties. Antimicrob. Ag. Chemother. 1967, p. 332-340.
23. Urlesberger, H., and E. Zechner. 1969. Klinische Erfahrungen bei chronischen Harnwegsinfekten mit Gentamycin. Wien. Med. Wochenschr. **44**:755-756.
24. Weinstein, M. J., G. M. Luedemann, E. M. Oden, G. H. Wagman, J. P. Rosselet, J. Marquez, C. T. Coniglio, W. Charney, H. Herzog, and J. Black. 1963. Gentamicin, a new antibiotic complex from Micromonospora. J. Med. Chem. **6**:463-464.
25. Wick, W. E., and J. S. Welles. 1968. Nebramycin, a new broad-spectrum antibiotic complex. IV. In vitro and in vivo laboratory evaluation. Antimicrob. Ag. Chemother. 1967, p. 341-348.