ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1980, p. 707-714
0066-4804/80/04-0707/08$02.00/0

Vol. 17, No. 4

Prospective, Randomized Trial of Netilmicin and Amikacin, with Emphasis on Eighth-Nerve Toxicity

MICHAEL BARZA,* MICHAEL W. LAUERMANN,† FRANCIS P. TALLY, AND SHERWOOD L. GORBACH

Department of Medicine, Infectious Disease Division, Tufts-New England Medical Center, Boston, Massachusetts 02111

The toxicity of netilmicin was compared with that of amikacin in a randomized, prospective trial in 90 adults with a variety of serious gram-negative infections. There was no instance of antibiotic-related nephrotoxicity in the group given amikacin and only one instance in the group given netilmicin. Cochlear toxicity, as measured by a change in audiogram, occurred in 4/14 (28.5%) of the amikacin recipients and 3/19 (15.8%) of the netilmicin recipients. Vestibular toxicity, as determined by a change in ice-water calorics, was noted in 3/16 (19%) of the amikacin-treated patients and 0/15 of the netilmicin-treated individuals. Despite the trend toward lesser ototoxicity with netilmicin, the differences between the drugs were not statistically significant. There was, however, a significant association between male sex and the development of ototoxicity. Although many patients could not be evaluated for efficacy, there did not appear to be any difference in the therapeutic activity of the two drugs.

Netilmicin, a semisynthetic analog of sisomicin, is similar to other aminoglycosides in its antibacterial spectrum (16, 21). Preliminary studies indicate that the drug is effective in treating gram-negative infections in humans (5, 21). However, netilmicin is severalfold less nephrotoxic than gentamicin, tobramycin, or amikacin in rats (1, 14), less cochleotoxic than gentamicin in guinea pigs (4), and less vestibulotoxic than gentamicin in cats (16). Therefore, we wished to compare the toxicity of netilmicin with that of an established aminoglycoside in a prospective, randomized fashion. We chose amikacin for this comparison because it possesses useful activity against strains resistant to other aminoglycosides (19), while its toxicity is essentially identical to that of gentamicin (10, 12, 20).

MATERIALS AND METHODS

Adult patients in the medical or surgical services of Tufts-New England Medical Center Hospital were eligible for the study if they were believed to have a serious infection for which an aminoglycoside antibiotic was indicated. Reasons for exclusion included pregnancy, allergy to aminoglycosides, or recent antimicrobial therapy likely to be effective against the infection. Many patients were enrolled before the presence of bacterial infection had been proven or the infecting organism had been characterized.

After informed consent had been obtained, a card was drawn from a set of sequentially numbered envelopes by which the patient was assigned to receive netilmicin or amikacin. The dosage of netilmicin was 2.5 mg/kg every 8 h intravenously over 30 to 60 min, or intramuscularly; this was usually reduced within 2 days to 2 mg/kg every 8 h. Amikacin was given in a dosage of 5 mg/kg every 8 h. These regimens were modified according to the state of renal function and serum concentrations of antibiotic. An effort was made to produce peak serum levels of 6 to 9 μg/ml for netilmicin and 15 to 25 μg/ml for amikacin.

The duration of therapy was determined by the attending physicians in conjunction with the consultant in infectious diseases. The following were considered valid reasons for discontinuing the antibiotic before completion of therapy: (i) failure to respond satisfactorily within 2 to 3 days; (ii) evidence that the pathogen was resistant to the aminoglycoside or could be adequately treated with a less toxic antibiotic, usually a penicillin or cephalosporin; (iii) the occurrence of suprainfection caused by a resistant organism; and (iv) evidence of aminoglycoside toxicity or allergy.

Evaluation of efficacy. Clinical responses were characterized as follows: complete resolution; improvement of signs and symptoms; failure; and indeterminate.

The bacteriological response was evaluated on the basis of gram-stained smears and cultures of body fluids and exudates as well as cultures of blood. Specimens were obtained immediately before, during, and after treatment. The bacteriological responses were defined as follows: elimination, marked reduction in numbers, and persistence of the infecting organism(s). Suprainfection was recognized by the finding of a new organism causing infection, as opposed to colonization.

Susceptibility testing was performed on isolates obtained before, during, and after completion of therapy. The standard antibiotic disk diffusion technique (Kirby-Bauer method) and twofold broth dilution pro-

† Present address: 1045 Atlantic Ave., Suite 902, Long Beach, CA 90813.

cedures in Mueller-Hinton broth were used (21). Both the minimum inhibitory concentration and minimum bactericidal concentration were determined by the latter method.

Evaluation of toxicity. Patients were considered assessable for toxicity if they received at least 72 h of treatment. The following routine measurements were done at the beginning and end of therapy: hemoglobin, hematocrit, and leukocyte count and differential; serum glutamic oxalacetic transaminase, alkaline phosphatase, bilirubin, electrolytes, creatinine concentration, and blood urea nitrogen; and microscopic urinalysis. In most patients these tests were repeated at frequent intervals during therapy.

The possibility of nephrotoxicity was considered when the serum creatinine concentration increased by at least 0.5 mg/dl over the base line during therapy.

Patients were observed closely for the occurrence of symptomatic eighth-nerve toxicity, including deafness, tinnitus, and dizziness. Pure-tone audiometry was requested within 48 h of the onset of therapy, every 3 to 4 days during therapy, and within 48 h of the end of therapy. Late posttreatment audiograms were obtained in some individuals. The majority of audiometric tests were performed at bedside because the patients were too ill to be moved to a soundproof room. Auditory toxicity was diagnosed if there was a decrease in perception of at least 15 dB in one or both ears at any frequency. Patients in whom initial audiograms could not be obtained were excluded from assessment unless audiograms performed during and at the end of therapy were normal, in which case they were considered to have experienced no auditory toxicity. Many patients could not be evaluated because of high ambient noise levels (e.g., in intensive-care units) or inability to cooperate.

Vestibular function was examined by means of ice-water caloric responses. These studies were performed by one of several otolaryngological consultants at approximately the same times as audiometric testing was done. The interpretation of the response as normal or abnormal was based upon the judgment of this consultant. In a few patients, electronystagmography was performed.

RESULTS

Ninety patients were treated, 42 with amikacin and 48 with netilmicin. Fifty-eight subjects (64%) were men. Many patients had severe underlying diseases, including malignancy or vascular disease, failure of major organ systems, or recent surgery. Most received other drugs concurrently, including antibiotics, immunosuppressive agents, and diuretics.

Efficacy. Sixty-three patients had proven bacterial infection. The sites of these infections and the most common pathogens isolated are summarized in Tables 1 and 2. In addition to the 27 patients in whom bacterial infection could not be proven, there were others in whom the response to therapy for a surmised infection could not be evaluated. In all, there were 73 patients in whom the clinical response to the aminoglycoside could not be assessed (Table 3). Nonetheless, the results in these 73 individuals were satisfactory, except for one who died shortly after admission to the hospital in septic shock.

TABLE 1. *Site of infections in 90 patients*

Site of bacterial infection	No. of patients[a]
None proven	27
Respiratory	17
Bone and soft tissue	21
Bacteremia	17
Urinary tract	7
Hepatobiliary	2

[a] One patient had two infections, respiratory and soft tissue.

TABLE 2. *Major infecting organism in 90 patients*

Major infecting organism	% of proven infections
Pseudomonas aeruginosa	35
Escherichia coli	16
Enterobacter sp.	8
Serratia marcescens	8
Klebsiella pneumoniae	3
Proteus sp.	3

TABLE 3. *Patients excluded from efficacy assessment*

Exclusions from efficacy assessment	No. of patients excluded
Treatment for less than 72 h	11
Insufficient bacteriological data	10
Concomitant administration of other potentially effective antibiotics	26
Bacterial infection not proven	27[a]
Initial bacterial resistance	2

[a] Three of these patients were also treated for <72 h. Thus, a total of 73 patients could not be evaluated for efficacy.

Among 17 patients (18 infections) in whom the efficacy of the aminoglycoside could be assessed, the results were satisfactory in all but five. There was failure to control the original infection in three individuals, two of whom were treated with amikacin and one with netilmicin; suprainfection was also present in one of these. In the fourth patient, suprainfection with a resistant *Escherichia coli* occurred during netilmicin therapy. In the fifth, an initially susceptible *Pseudomonas aeruginosa* became resistant during treatment with netilmicin.

Nephrotoxicity. Sixty-nine patients could be evaluated for this adverse effect. Among 32 given amikacin, 4 experienced significant (>0.5 mg/dl)

increases in serum creatinine concentration during treatment. In two, the peak concentration did not exceed 1.3 mg/dl. In the third, it increased from 1.5 to 2.1 mg/dl, but spontaneously declined to 1.4 mg/dl by day 5 of therapy. The fourth patient experienced a moderate increase in serum creatinine concentration; however, at autopsy, this was attributed to intrarenal hemorrhage due to severe thrombocytopenia. Thus, no patient was believed to have amikacin-related nephrotoxicity.

Among 37 subjects receiving netilmicin, three experienced increases in serum creatinine concentration. In one patient who was begun on therapy while recovering from acute tubular necrosis, the serum creatinine level fluctuated between 1 and 2 mg/dl. Another person was diagnosed as having hepatorenal syndrome. Neither was considered to have antibiotic-related nephrotoxicity. A third patient, who was treated with netilmicin for 39 days, experienced a rise in serum creatinine concentration from 1.0 to 2.1 mg/dl. He was given carbenicillin concurrently and exhibited signs of allergy to this drug. Nonetheless, his renal dysfunction was considered probably related to the netilmicin. He was the only subject in this study believed to have aminoglycoside-related nephrotoxicity.

Auditory toxicity. Fifteen patients receiving amikacin and 19 receiving netilmicin could be adequately assessed for auditory toxicity. Five of the 15 amikacin recipients (33.33%) experienced decreases of at least 15 dB on at least one occasion; however, in patient 47, the abnormalities were only at low frequencies and were considered likely to be due to room noise. If that patient is excluded entirely, the rate of auditory toxicity with amikacin becomes 4/14 (28.5%). Three patients receiving netilmicin (3/19 [15.8%]) experienced audiographic changes. Salient features of patients with auditory toxicity are summarized in Table 4. The rates of audiographic decreases with amikacin and netilmicin were not significantly different (Table 5) by the chi-square test using 2×2 contingency tables with Yates' correction (χ^2_c) whether the rate of amikacin-related toxicity was regarded as 4/14 or 5/15.

None of the patients reported a decrease in hearing. However, two complained of tinnitus. One (patient 89) is described in Table 4. The other, a 58-year-old man treated with netilmicin for 7 days, noted intermittent tinnitus during treatment. Because he had no change in his audiograms, which showed stable high-frequency sensorineural loss throughout his course of therapy, he was not considered to have netilmicin-related cochlear damage.

Vestibular toxicity. Sixteen patients receiving amikacin and 15 receiving netilmicin had adequate caloric testing to permit assessment of vestibular toxicity. In three, all receiving amikacin, the responses were considered abnormal by the otolaryngological consultant. Patient 4 (Table 4) was first noted to have abnormal responses on day 7 of therapy. A second patient, a 51-year-old man with Hodgkin's disease and radiation pneumonitis, received amikacin for 7 days (total dose, 5,950 mg) together with carbenicillin. There was a bilateral decrease in caloric response by day 6, accompanied by an abnormal electronystagmogram, but this had improved 2 days after the end of therapy. The third patient was a 57-year-old man with chronic lymphocytic leukemia and septic arthritis. He was treated with amikacin for 40 days (total dose, 27,850 mg) and carbenicillin. One month after treatment, abnormal caloric responses were detected bilaterally. He was considered to have probable late-developing vestibular toxicity due to amikacin.

Only one patient experienced vertigo. It began at the time of ice-water caloric testing on day 4 of netilmicin therapy and persisted for 1 week. It was attributed by the patient to the procedure. The test results were normal, and the patient refused to undergo further examinations. This was not considered an instance of drug toxicity.

The rates of vestibular toxicity with amikacin (3/16 [19%]) and with netilmicin (0/15 [0%]) were not significantly different (Table 5). The chi-square test of heterogeneity showed that the rates of auditory and vestibular toxicity for each drug could be combined. When this was done, the overall rates of eighth-nerve toxicity for amikacin and netilmicin were still not significantly different (Table 5), although there was a suggestive trend.

Factors potentially contributing to eighth-nerve toxicity. Having failed to demonstrate a significant effect of the particular aminoglycoside upon the rate of eighth-nerve toxicity, we proceeded to examine other factors that might contribute. Although patient 73, and possibly patients 77 and 89, had relatively high peak or trough serum levels of amikacin, the other individuals described in Tables 1 to 3 did not have demonstrably high concentrations in the limited number of measurements made. We found no significant difference in terms of age, duration of aminoglycoside therapy, or previous cochlear damage (abnormal initial audiogram) between patients with auditory toxicity and those with no change in audiograms (Table 5). Four patients who developed auditory toxicity, and eight who did not, had abnormal initial audiograms. In one other audiotoxic patient, the first audiogram was abnormal, but was obtained on day 7 of therapy so that it could not be

TABLE 4. *Characteristics of patients with auditory toxicity*

Drug	Patient no.	Age (yr), sex	Renal disease[a]	Concomitant antibiotic or diuretic	Duration of treatment (days)	Total dose (mg)	Serum levels (μg/ml)		Manifestations of auditory toxicity[b]
							Peak	Trough	
Netilmicin	32	53, M	No	Carbenicillin Cefazolin	12	7,000	6.6 8.0	1.6 1.4	15 dB (R ear) at 8,000 Hz, day 7 15 dB (R ear) at 4,000 Hz, day 13 Returned to base line by 2 mo
	40	67, M	Cr_s = 2.0	Carbenicillin Clindamycin	39	13,900	5.1 5.8 5.9		30 dB (R ear) at 8,000 Hz, day 20 Persistent 1 mo after treatment
	92	62, M	Cr_s = 8.0	Oxacillin Clindamycin	10	790	2.3	1.8	25–30 dB (L ear) at 500, 1,000, 4,000, and 6,000 Hz, day 9
Amikacin	4	66, M	Cr_s = 1.5	Carbenicillin Ethacrynic acid	7	2,845	6.9 7.7	5.0 4.6	15–20 dB (R ear) at 2,000 and 4,000 Hz, day 5 20–30 dB (R ear) at 2,000 and 4,000 Hz, day 5 Persistent 16 days after treatment
	47	47, M	No	Carbenicillin	15	18,900	14.8		15 dB R ear at 250 Hz day 15 20 dB R ear at 500 Hz day 15 (Room noise may have affected results)
	72	65, M	No	Cefazolin Hydrochlorothiazide	19	16,475	30, 31 22, 54	13, 12 12, 19	20 dB (R ear) at 8,000 Hz, day 25 20 dB (L ear) at 8,000 Hz, day 25
	77	57, M	No	Ticarcillin	40	27,850	38, 26 25, 15 20	<4, <4 4, 1.7	15 dB (no response) (R ear) at 8,000 Hz, day 24 Returned to base line by day 32
	89	52, M	No	Carbenicillin	48	57,450	12, 15 34, 45 22	3, 5 4, 9 10, 11	25 dB R ear at 8000 Hz day 22 20 dB R ear at 2000 Hz day 34 15 dB R ear at 4000 Hz day 34 More severe changes developed over next 2 weeks

[a] Cr_s, Serum creatinine concentration (milligrams per deciliter).
[b] Loss in hearing. R, Right; L, left.

TABLE 5. *Influence of selected variables on the occurrence of auditory toxicity and vestibular toxicity*

Factor	Toxicity						Statistical comparison
	Auditory			Vestibular			
	Amikacin	Netilmicin	Combined	Amikacin	Netilmicin	Combined	
Aminoglycoside	4/14 (28.5%)	3/19 (15.8%)		3/16 (19%)	0/15 (0%)		Combined auditory and vestibular toxicity: amikacin, 7/30 (23%); netilmicin, 3/34 (9%)
	NS, $\chi^2_c = 0.22$			NS, $\chi^2_c = 1.48$			
Age of patient			Mean age of toxic patients, 57.7 yr				NS, $\chi^2_c = 1.54$ Combined drugs, mean age of 26 non-cochleotoxic patients: 50.8 yr Not significantly different from toxic patients ($P >$ 0.20 by Mann-Whitney test)
Duration of treatment			Mean duration in toxic patients, 20.1 days				Combined drugs, mean duration in 26 non-cochleotoxic patients; 10.7 days Not significantly different from toxic patients ($P =$ 0.1–0.2 by Mann-Whitney test)
Abnormal initial audiograms			4/7 toxic patients				Combined drugs, 8/25 non-cochleotoxic patients Not significantly different from toxic patients ($\chi^2_c =$ 0.63, $P > 0.25$)
Concomitant carbenicillin or ticarcillin			5/7 toxic patients				Combined drugs, 8/26 non-chochleotoxic patients Not significantly different from toxic patients ($\chi^2_c =$ 2.19, $P > 0.10$)
Male sex			7/7 toxic patients			3/3 toxic patients	Combined drugs and types of toxicity, 10/10 toxic patients vs 33/54 nontoxic patients Significant difference ($\chi^2_c =$ 4.63, $P < 0.05$)

[a] Data were combined only if not significantly different by the chi-square test of heterogeneity. χ^2_c, Chi-square test using 2 × 2 contingency tables with Yates' corrections. NS, Not statistically significant.

determined whether there was preceding cochlear damage (patient 47). In most instances, the abnormal initial audiograms showed sensorineural loss which was presumed to be due to presbyacusis. Patient 72 was believed to have a noise-related deficit. There was also no association of auditory toxicity with the presence of major vascular disease (data not shown). Two of three patients with netilmicin-related auditory toxicity and one of four with amikacin-related damage had renal impairment. A test of heterogeneity showed that groups could not be combined and the netilmicin patients were too few to permit statistical analysis. Five of the 7 (71%) patients with auditory toxicity received carbenicillin or ticarcillin concomitantly, while only 8 of 26 (31%) nontoxic patients received these agents. However, the difference was not statistically significant (Table 5).

The only characteristic that showed a significant association with the development of eighth-nerve damage in this study was sex. All seven patients with cochlear toxicity and all three with vestibular damage were men. Although the frequency of maleness was not significantly different for auditory toxicity (7/7 toxic patients versus 16/26 nontoxic patients were male; $\chi^2_c = 2.21$; $P > 0.10$) or vestibular toxicity (3/3 toxic patients versus 6/13 nontoxic patients were male; $\chi^2_c = 0.57$; $P > 0.25$), the test of heterogeneity showed the two forms of toxicity could be combined. When this was done, there was a significant contribution of male gender (Table 5).

Other adverse reactions. Five patients developed allergic manifestations (rash, eosinophilia, and recrudescence of fever) in conjunction with the administration of the aminoglycosde; four were receiving amikacin; and one was receiving netilmicin. However, in only one instance was it considered likely that the aminoglycoside antibiotic (amikacin) was responsible for the reaction.

Three patients exhibited mild increases in liver enzymes during the course of therapy. The relation to aminoglycoside therapy was considered doubtful in each instance.

DISCUSSION

The aminoglycoside antibiotics most commonly used in the United States today are gentamicin, tobramycin, and amikacin. These do not appear to differ significantly in efficacy or toxicity in humans (10, 12, 20). However, a recent study found that tobramycin was significantly less nephrotoxic than gentamicin (C. R. Smith, J. Lipsky, O. Laskin, D. Hellmann, D. Mellits, J. Longstreth, and P. Lietman, Program Abstr. 11th Int. Congr. Chemother. and Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 947, 1979).

The efficacy of a new congener, netilmicin, has been compared with that of other aminoglycosides in prospective randomized trials. Love and colleagues, studying febrile granulocytopenic patients with cancer, found no difference among gentamicin, amikacin, or netilmicin when combined with ticarcillin (12). Eden et al. reported netilmicin and gentamicin to be of similar efficacy in patients who were critically ill with a variety of infections (6), and Loveless and coworkers had similar results in the treatment of pyelonephritis (13). Netilmicin and amikacin were equally effective in the therapy of complicated urinary tract infections (15), as were netilmicin and tobramycin (8).

The present study was designed primarily to compare the toxicity, rather than efficacy, of netilmicin and amikacin. Indeed, efficacy could not be reliably determined in the majority of patients, largely on account of the concomitant administration of other potentially effective antibiotics and because of insufficient bacteriological documentation. However, among the 63 patients with proven bacterial infection, there were three instances of failure to control the infection, two episodes of suprainfection, and one instance in which the infecting strain of *P. aeruginosa* became resistant during therapy. Overall, no difference in efficacy between the two drugs was apparent in this study.

There was only one instance of nephrotoxicity which could be attributed to the aminoglycoside in this investigation. Previous reports, using criteria identical to ours, found rates of nephrotoxicity ranging from 2 to 8% with these same drugs (12, 20). We have no explanation for the comparatively low rate of renal damage (1/69 = 1.4%) encountered in the present study. Others have found no difference between netilmicin and amikacin (12, 15), or between netilmicin and gentamicin (6, 13), in their nephrotoxic potential.

The rates of auditory toxicity, as measured by at least a 15-dB decrease in audiometric response, were 28.5% for amikacin and 15.8% for netilmicin. Although the difference was almost twofold, it was not statistically significant. This may simply reflect the relatively small numbers of patients who could be adequately evaluated for this adverse effect. If the same rates of auditory toxicity (28.5 and 15.8%) continued to be observed, 180 patients would have to be studied audiometrically to achieve statistical significance at the $P < 0.05$ level, an increase of more than fivefold over our present sample size. Love et al., who required at least a 20-dB decrease

over the base line, and Maigaard and co-workers, who accepted a 5-dB deficit as evidence of audiometric damage, found no difference between netilmicin and other aminoglycosides (12, 15). In contrast, Bock et al., while providing no definition of toxicity, reported audiographic deterioration in 6/16 patients treated with amikacin as opposed to 1/19 treated with netilmicin ($P = 0.05$) (B. V. Bock, P. H. Edelstein, and R. D. Meyer, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 304, 1979). Thus, further study will be necessary to determine whether or not netilmicin is in fact less cochleotoxic than other aminoglycosides.

We found no significant difference in vestibular toxicity between netilmicin and amikacin; however, as with auditory toxicity, a trend was suggested which merits continued investigation. Although ice-water caloric testing is not as effective as bithermal testing (12) or electronystagmography, we have encountered no other reports in which objective methods were used to compare vestibular toxicity of currently used aminoglycosdes.

In attempting to discover factors which might predispose to the development of eighth-nerve damage, we performed several retrospective analyses, recognizing the hazards inherent in this approach (17). Combining the rates of vestibular and auditory toxicity still did not disclose a significant difference between amikacin (23%) and netilmicin (9%). Several factors, including the age of the patient, duration of treatment, and abnormal initial audiogram, failed to show a significant association with the development of auditory impairment. Concomitant administration of carbenicillin or ticarcillin was suggestively, but not significantly, associated with auditory toxicity. An unexpected finding was that 10/10 patients with nerve damage (auditory or vestibular) were male as opposed to 33/54 nontoxic patients ($P < 0.05$). Neither factor has, to our knowledge, been reported previously to contribute to eighth-nerve damage due to aminoglycosides (3, 7, 9, 11, 18). However, a recent study in rats found a significantly greater susceptibility of males than females to the nephrotoxic potential of gentamicin (R. A. Parker, W. M. Bennett, C. E. Plamp, D. C. Houghton, D. N. Gilbert, and G. A. Porter, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 938, 1979). A similar phenomenon has also been reported in humans; however, the effect was not quite statistically significant (C. S. Goodwin, Program Abstr. 11th Int. Congr. Chemother. and Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 944, 1979).

The data in the present study do not permit us to come to a firm conclusion regarding the comparative efficacy of netilmicin and amikacin. They do suggest, however, that the two drugs are of low but similar nephrotoxic potential. Netilmicin showed a trend toward lesser cochlear as well as vestibular toxicity; however, the differences between agents were not statistically significant.

ACKNOWLEDGMENT

We thank Robert Hirsch for performing the statistical analyses.

LITERATURE CITED

1. **Barza, M., V. Pinn, P. Tanguary, and T. Murray.** 1978. Nephrotoxicity of newer cephalosporins and aminoglycosides alone and in combination in a rat model. J. Antimicrob. Chemother. 4(Suppl. A):59–68.
2. **Becker, G. D.** 1979. The screening value of monothermal caloric tests. Laryngoscope 89:311–314.
3. **Black, R. E., W. K. Lau, R. J. Weinstein, L. W. Young, and W. L. Hewitt.** 1976. Ototoxicity of amikacin. Antimicrob. Agents Chemother. 9:956–961.
4. **Brummett, R. E., K. E. Fox, R. T. Brown, and D. L. Himes.** 1978. Comparative ototoxic liability of netilmicin and gentamicin. Arch. Otolaryngol. 104:579–584.
5. **Buckwold, F. J., A. R. Ronald, B. Lank, L. Thompson, L. Fox, and G. K. M. Harding.** 1979. Clinical efficacy and toxicity of netilmicin in the treatment of gram-negative infections. Can. Med. Assoc. J. 120:161–167.
6. **Eden, T., P. Skansberg, and K. Haeger.** 1978. Netilmicin in severe infections: a randomized comparison with gentamicin. Curr. Therap. Res. 24:96–107.
7. **Fee, W. E., Jr., V. Vierra, and G. R. Lathrop.** 1978. Clinical evaluation of aminoglycoside toxicity: tobramycin versus gentamicin, a preliminary report. J. Antimicrob. Chemother. 4(Suppl. A):31–36.
8. **Hoyme, U., and P. O. Madsen.** 1978. Netilmicin and tobramycin in the therapy of complicated urinary tract infections, p. 987–989. *In* W. Siegenthaler and R. Luthy (ed.), Current chemotherapy. Proceedings of the 10th International Congress of Chemotherapy, vol. II. American Society for Microbiology, Washington, D.C.
9. **Jackson, G. G., and G. Arcieri.** 1971. Ototoxicity of gentamicin in man: a survey and controlled analysis of clinical experience in the United States. J. Infect. Dis. 124(Suppl.):S130–S137.
10. **Keating, M. J., G. P. Bodey, M. Valdivieso, and V. Rodriguez.** 1979. A randomized comparative trial of three aminoglycosides—comparison of continuous infusions of gentamicin, amikacin and sisomicin combined with carbenicillin in the treatment of infections in neutropenic patients with malignancies. Medicine (Baltimore) 58:159–170.
11. **Lane, A. Z., G. E. Wright, and D. C. Blair.** 1977. Ototoxicity and nephrotoxicity of amikacin. An overview of phase II and phase III experience in the United States. Am. J. Med. 62:911–918.
12. **Love, L. J., S. C. Schimpff, D. M. Hahn, V. M. Young, H. C. Standiford, J. F. Bender, C. L. Fortner, and P. H. Wiernik.** 1979. Randomized trial of empiric antibiotic therapy with ticarcillin in combination with gentamicin, amikacin or netilmicin in febrile patients with granulocytopenia and cancer. Am. J. Med. 66:603–610.
13. **Loveless, M. O., S. Kohlhepp, J. Jackson, and D. N. Gilbert.** 1979. A prospective study of gentamicin and netilmicin in the treatment of pyelonephritis. Curr. Therap. Res. 25:595–602.
14. **Luft, F. C., M. N. Yum, and S. A. Kleit.** 1976. Comparative nephrotoxicities of netilmicin and gentamicin in rats. Antimicrob. Agents Chemother. 10:845–849.

15. **Maigaard, S., N. Frimodt-Moller, and P. O. Madsen.** 1978. Comparison of netilmicin and amikacin in treatment of complicated urinary tract infections. Antimicrob. Agents Chemother. **14**:544–548.
16. **Miller, G. H., G. Arcieri, M. J. Weinstein, and J. A. Waitz.** 1976. Biological activity of netilmicin, a broad-spectrum semisynthetic aminoglycoside antibiotic. Antimicrob. Agents Chemother. **10**:827–836.
17. **Nelson, R. B.** 1979. Are clinical trials pseudoscience? 1979. Forum Med. (Engl. Ed.) **2**:594–600.
18. **Neu, H. C., and C. L. Bendush.** 1976. Ototoxicity of tobramycin: a clinical overview. J. Infect. Dis. **134**(Suppl.):S206–S218.
19. **Price, K. E., M. D. DeFuria, and T. A. Pursiano.** 1976. Amikacin, an aminoglycoside with marked activity against antibiotic-resistant clinical isolates. J. Infect. Dis. **134**(Suppl.):S249–S261.
20. **Smith, C. R., K. L. Baughman, C. Q. Edwards, J. F. Rogers, and P. S. Lietman.** 1977. Controlled comparison of amikacin and gentamicin. N. Engl. J. Med. **296**: 349–353.
21. **Snydman, D. R., F. P. Tally, S. H. Landesman, M. Barza, and S. L. Gorbach.** 1979. Netilmicin in gram-negative bacterial infections. Antimicrob. Agents Chemother. **15**:50–54.