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Prospective Comparative Study of Efficacy and Toxicity of Netilmicin and Amikacin

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Eighty patients were treated with either amikacin or netilmicin in a prospective randomized study of serious gram-negative bacillary infections, including 11 due to gentamicin-resistant pathogens. Thirty-six treated with netilmicin and 35 treated with amikacin were evaluable for efficacy or toxicity, or both. The overall groups differed significantly only in age. There were no significant differences in efficacy of the two drugs. There were no statistically significant differences at the 95% level between the netilmicin group and the amikacin group with respect to nephrotoxic reactions (38 versus 28%, respectively) or ototoxic reactions (9 versus 25%, respectively). Further comparative trials of netilmicin and other aminoglycosides appear warranted before it is widely used.

Netilmicin is a new aminoglycoside active in vitro against a wide variety of *Enterobacteriaceae* and *Pseudomonas aeruginosa* (4, 12, 17, 21, 23, 24). It is resistant to two of the enzymes that inactivate gentamicin (17, 21) and has significantly less ototoxicity (19) and nephrotoxicity than gentamicin in experimental animals (7, 13, 15). In open clinical trials, it has been therapeutically effective and appears to have less cochlear toxicity than other aminoglycosides (2, 5, 11, 12, 16, 22, 29, 30). In some clinical studies netilmicin has exhibited minimal nephrotoxicity (11, 16), whereas in others nephrotoxicity has been appreciable (2, 5, 12, 22, 29, 30). Amikacin is effective in therapy of patients with serious gram-negative infections, including those due to gentamicin-resistant organisms (18, 19). It appears to have minimal nephrotoxicity (27, 28) but somewhat more ototoxicity (18).

A controlled comparison of efficacy and toxicity of netilmicin and amikacin appeared warranted, particularly in a setting where there is a high incidence of serious infections with gentamicin-resistant pathogens (20). The results of such a controlled prospective randomized trial are set forth in this report.

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MATERIALS AND METHODS

Eighty patients with serious gram-negative bacillary infections were randomized prospectively by card allocation with sealed envelopes to receive amikacin or netilmicin. All patients were hospitalized at Veterans Administration Wadsworth Medical Center during the period from February 1977, through November 1978. Informed consent was obtained from patients or the next of kin. Criteria for inclusion in the study included temperature ≥38.3°C and evidence on Gram stain or culture of infection due to gram-negative bacilli. Patients with a neutrophil count <1,000/mm^3 were excluded. Patients who had received gentamicin within the previous 7 days were included only if they had gentamicin-resistant organisms and had failed to respond to gentamicin therapy. Other antibiotics were not administered except when penicillin, oxacillin, or clindamycin was given for infections with anaerobes or gram-positive organisms. Carbenicillin was added to the regimen only after there had been no clinical or bacteriological response to the aminoglycoside.

Appropriate cultures were obtained before, during, and after antibiotic therapy and, whenever possible, at the follow-up visit 4 to 6 weeks later. Serotyping and repeat transtracheal aspirations were not performed. Blood cultures were generally obtained immediately before initiation of therapy.

Criteria for septicemia were positive blood culture with fever, chills, or hypotension (blood pressure ≤ 90/60 mm of Hg). Criteria for the diagnosis of pneumonia included (i) roentgenological evidence of a new pulmonary infiltrate and (ii) leukocytes and gram-negative bacilli in secretions obtained by transtracheal aspiration or from an endotracheal tube. Organisms isolated from coughed sputum were considered to be etiological only when they were simultaneously recovered from blood or pleural fluid. Criteria for the other infections were the same as in previous studies (5, 18).

Criteria for clinical (cure, improved, failed) and bacteriological evaluation have been listed previously (5, 18) but modified so that if an adverse reaction made it necessary to stop the drug, or if carbenicillin was added to the regimen, a clinical failure was judged.

Patients were evaluable for efficacy or toxicity, or both, if they received more than 72 h of therapy and if pretreatment cultures grew aerobic gram-negative

bacilli not susceptible to concurrent antibiotics. One patient with negative cultures received therapy for 5 days.

Amikacin sulfate (Bristol Laboratories, Syracuse, N.Y.) was supplied as an aqueous solution in 500-mg vials of 2 ml each. It was given initially at a dose of 7.5 mg per kg of lean body weight either intravenously in 5% dextrose in water over 30 min or intramuscularly. Subsequent doses were given every 12 h. In patients with renal insufficiency, doses were reduced according to estimated creatinine clearance (3), a nomogram (26), and results of serum levels. Patients undergoing chronic hemodialysis received 7.5 mg/kg initially and then 3.5 to 5.0 mg/kg after each dialysis. One patient undergoing peritoneal dialysis received 7.5 mg/kg initially and then 10 to 15 mg in each liter of dialysis fluid. Netilmicin (Schering-Plough Research Division, Bloomfield, N.J.) was supplied as 2-ml vials containing 100 mg/ml and it was administered intravenously or intramuscularly. The initial dose was 2.0 or 2.5 mg/kg, and then 2.0 mg/kg every 8 h for patients with normal renal function. Doses were adjusted on the basis of estimated creatinine clearances and a gentamicin nomogram (3, 8). One patient undergoing peritoneal dialysis received an initial parenteral dose and then 8 mg of netilmicin per liter in the dialysis fluid. One patient on hemodialysis was given 1.0 mg/kg after each dialysis as a maintenance dose.

A complete blood count with differential leukocyte count, blood urea nitrogen, serum creatinine, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, lactic dehydrogenase, and bilirubin was obtained before therapy, every 2 or 3 days while on therapy, and after therapy.

Peak serum levels were obtained 1 h after the infusion, and trough levels were obtained 0.5 before the next dose. Patients on hemodialysis had serum drawn immediately predialysis, postdialysis, and 1 h after the dose was given. Levels were generally repeated every 3 days, or more frequently in patients with renal insufficiency. Levels were measured by radioimmunoassay or by the agar diffusion method, using *Klebsiella pneumoniae* or *Bacillus globigii* as the reference strain (5, 18). Mean standard deviations were 0.57 μg/ml for amikacin determinations and 0.48 μg/ml for netilmicin determinations.

Susceptibility testing was performed by a standardized disk testing method (1), using 10-μg amikacin and netilmicin disks, and by the agar plate dilution method for *Enterobacteriaceae* (6). Control strains were *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC no. 27853. Freeze-thaw extraction of the agar medium was performed. The mean magnesium content of the liquid extracted from the medium was 2.55 mg/100 ml, and mean calcium content was 2.30 mg/100 ml, as measured by atomic absorption spectrophotometry. *Pseudomonas* species were tested by the broth dilution method (6). The mean magnesium content of the broth was 0.28 mg/100 ml, and mean calcium content was 0.28 mg/100 ml. Organisms were considered resistant to gentamicin or netilmicin if the minimal inhibitory concentration (MIC) was ≥16 μg/ml and resistant to amikacin if the MIC was ≥32 μg/ml (17, 19, 20).

Serial audiograms were obtained in a soundproof room whenever possible in responsive patients at the beginning of therapy, once a week during therapy, and after its completion. A Grason-Statler 1701 (Grason-Statler Co., West Concord, Mass.) or a Maico MA24 dual-channel diagnostic audiometer (Maico, Minneapolis, Minn.) was used. Otherwise audiograms were performed at the bedside with a Maico model MA-20 portable audiometer. Patients were questioned daily by an investigator for tinnitus, fullness in the ears, subjective hearing loss, and vertigo and examined for nystagmus. A 10-decibel bilateral drop or a 15-decibel unilateral drop from 250 to 8,000 Hz on successive testing was interpreted as a significant change in patients who had not received ototoxic drugs within 7 days.

Nephrotoxicity was defined as an increase in serum creatinine of >0.4 mg/100 ml if the base-line creatinine was <3.0 mg/100 ml and an increase of >0.9 mg/100 ml if the base-line creatinine was >3.0 mg/100 ml (27, 28). If other factors were present such as shock, furosemide, congestive heart failure, other aminoglycosides, sulfonamides, or cephalosporins, the reaction was judged possible or doubtful. The cause of other types of adverse reactions was evaluated on the basis of other drugs administered and underlying disease.

Differences in proportions were analyzed by a chi-square test with Yates correction. Differences in means were analyzed by Student's *t* test.

RESULTS

Overall results. Data for the evaluable patients are included in Table 1. Thirty-six patients treated with netilmicin and 35 treated with amikacin were evaluable for efficacy, toxicity, or both. The mean age was 64.0 ± 12.2 years in the netilmicin group and 56.5 ± 11.2 in the amikacin group. This was the only significant difference. Nine patients who could not be evaluated received the drug for less than 72 h; five in the netilmicin group and three in the amikacin group had no aerobic gram-negative bacilli isolated, and another in the amikacin group received a cephalosporin.

The results of therapy are noted in Table 2. Thirty-four patients treated with netilmicin were assessed for both criteria, and two with infections due to anaerobes were assessed for toxicity alone. The response rate for genitourinary tract infections (including seven patients who had bacteremia) was 21 of 22, or 95.4%, and the response rate for all other infections was 9 of 12, or 75%. The overall response rate was 30 of 34, or 88.2%. Five patients developed suprainfections; one had a urinary tract suprainfection with *Providencia stuartiii* which was netilmicin resistant (MIC = 32 μg/ml) and was treated successfully with kanamycin. No patients died during therapy, but three died with infection within 4 weeks after therapy from accompanying disease alone.

TABLE 1. *Comparison of patients receiving either netilmicin or amikacin*

Treatment	Patients				Duration of treatment (days)	Severity of illness[a]	No. of patients with:		
	No.	Age (yr)	Sex (no.)				Bacteremia	Shock[b]	Pretherapy gentamicin-resistant isolates
			Male	Female					
Netilmicin	36	64.0 ± 12.2[c] (35–90)[d]	35	1	11.1 ± 7.19[c]	3.1 ± 0.97	14	3	3
Amikacin	35	56.5 ± 11.2 (29–79)	34	1	11.5 ± 6.88	3.2 ± 0.73	17	10	8
P value	>0.10	<0.005	>0.10	>0.10	>0.10	>0.10	>0.10	0.06	>0.10

[a] An arbitrary enteger scale, with "4" being maximally ill and "1" being least ill.
[b] Blood pressure ≤90/60 mm of Hg and manifesting clinical signs of shock.
[c] Mean ± standard deviation.
[d] Range.

TABLE 2. *Overall clinical efficacy of netilmicin and amikacin*

Infection	Netilmicin (No.)					Amikacin (No.)				
	Cure	Improved	Cure or improved	Failure	Total	Cure	Improved	Cure or improved	Failure	Total
Septicemia[a]	9	2	11	3[b]	14	12	3	15	2	17
Genitourinary	7	8	15	0	15	2	3	5	1[c]	6
Pulmonary	0	1	1	1	2	0	0	0	2	2
Miscellaneous	2	1	3	0	3	4	3	7	1	8
All infections	17 (50%)	13 (38.2%)	30 (88.2%)	4 (11.8%)	34	14 (42.4%)	12 (36.4%)	26 (78.8%)	7 (21.2%)	33
Suprainfections[d]	2	1	3	2	5 (14.7%)	0	0	0	1	1 (3.0%)
Death[e]					6					9

[a] Includes all patients with septicemia. Twelve patients in the netilmicin group and 14 patients in the amikacin group were evaluated for one or more additional infections which are described in the text.
[b] Drug was stopped because of ototoxicity in one patient.
[c] Drug was stopped because of nephrotoxicity in one patient.
[d] One in the netilmicin group was due to a netilmicin-resistant gram-negative bacillus.
[e] While on therapy or before the follow-up visit at 4 to 6 weeks after therapy.

Thirty-three patients treated with amikacin were assessed for efficacy. The response rate in patients with genitourinary tract infections (including 5 who had bacteremia) was 9 of 11, or 81.8%, and for all others was 22 of 29, or 75.9%. The overall efficacy was 78.8%. One patient had a suprainfection with methicillin-resistant *Staphylococcus aureus* bacteremia which cleared. Two patients died during therapy, one from infection and one from extensive carcinoma. Seven patients expired soon after therapy, three from infection and four from accompanying disease.

Septicemia. Fourteen patients treated with netilmicin had septicemia (Table 2). In four, blood cultures drawn the previous day were positive, but those drawn just before antibiotic therapy (while the patients were still febrile) were negative. They were classified as bacteriologically indeterminant for septicemia; all responded clinically (two genitourinary tract infections, one pneumonia, one septic phlebitis). Of the ten other patients, the source was the genitourinary tract in five, biliary tract in two, and phlebitis, endocarditis, and undetermined in one each. Nine of the 14 patients with septicemia were cured, 2 were improved, and 3 failed to respond. One patient who failed had *E. coli* bacteremia from a biliary source, and the bacteremia cleared only after cefazolin was substituted. Another patient had bacteremia (during gentamicin therapy) with gentamicin-resistant *Serratia marcescens* (MIC > 128 μg/ml) from the genitourinary tract. He had positive blood cultures during netilmicin therapy, despite high mean peak (20.0 μg/ml) and trough (14.5 μg/ml) levels in the face of nephrotoxicity. The netilmicin MIC increased from 8 to 128 μg/ml during therapy. Clinical failure in endocarditis necessitated addition of carbenicillin, although blood cultures were negative during netilmicin therapy in another patient.

Seventeen patients treated with amikacin had septicemia. Four of these patients were indeterminant bacteriologically; all four responded to therapy (two urinary tract infections, one wound infection, and one septic phlebitis). Of the 13 other patients, the source was the genitourinary

tract, undetermined, and pneumonia (one had empyema) in three each, and wound, septic phlebitis, biliary tract, and pericarditis in one each. Twelve of the 17 patients were cured, 3 were improved, and 2 failed to respond to therapy. One patient who failed had pneumonia and empyema with two gentamicin-resistant organisms, *K. pneumoniae* and *P. aeruginosa*. He had repeatedly positive blood cultures with *K. pneumoniae* during therapy. The other patient had pericarditis due to *P. aeruginosa* and required the addition of carbenicillin because of clinical failure.

Genitourinary tract infections. All 15 patients treated with netilmicin for nonbacteremic urinary tract infections responded. Seven were cured. Of the eight who improved, three had a bacteriological cure but were reinfected, and five responded clinically but had a bacteriological failure (one *S. marcescens* netilmicin MIC = 32 μg/ml). In the amikacin group, two of the six patients were cured, and three improved (one cure with reinfection, one clinical improvement with bacteriological failure, and one patient improved but died from pulmonary disease after only 4 days of therapy). Amikacin was stopped after 72 h due to nephrotoxicity in the failure.

Pulmonary infections. Two patients treated with each antibiotic were evaluated for pulmonary infections exclusive of septicemia. One patient treated with netilmicin was critically ill with mediastinitis and empyema due to *S. marcescens* and failed to respond after 24 days of therapy. The other patient had empyema due to *K. pneumoniae* (and *Lactobacillus* species) and had marked improvement with netilmicin and clindamycin. Neither patient treated with amikacin for pneumonia responded; one had overwhelming infection due to *K. pneumoniae* and expired after only 48 h of therapy; the other patient was comatose and expired from recurrent aspiration.

Miscellaneous. One patient with septic arthritis and one with peritonitis were cured with netilmicin, and one with a wound infection was moderately improved. Eight patients received amikacin. Four had wound infections; two with intraabdominal abscesses and two with peritonitis also received clindamycin. All these patients responded except one patient with an intraabdominal abscess.

Serum levels. Mean peak serum level in the amikacin group was 23.9 μg/ml ± 7.4, and mean valley level was 4.7 μg/ml ± 3.8. Mean 1-h peak netilmicin level was 7.4 μg/ml ± 4.0, and mean valley level was 3.0 μg/ml ± 3.6. Predictable levels were attained initially in most patients by use of calculated creatinine clearances and the nomograms (21–23). Initial amikacin levels were within the desirable range (peak, 15 to 25 μg/ml; valley, ≤5 μg/ml) in 80% of patients. However, netilmicin levels were less reliable, and levels in the desirable range (peak, 4 to 8 μg/ml; valley, ≤2 μg/ml) were achieved in only 57% of patients. Netilmicin levels were above or below this range in approximately equal numbers of patients.

MIC results. Cumulative percent MIC results for *Enterobacteriaceae* and for *Pseudomonas* are shown in Fig. 1. *P. aeruginosa* or *P. fluorescens* group organisms were isolated from three patients in the netilmicin group and six in the amikacin group. For the *Enterobacteriaceae*, the geometric mean MICs were: gentamicin, 1.9 μg/ml; amikacin, 2.4 μg/ml; and netilmicin, 1.3 μg/ml.

Gentamicin-resistant organisms. Eleven patients had 12 pretherapy isolates resistant to gentamicin. All had severe underlying disease, and seven had failed to respond to gentamicin therapy: two in the netilmicin and five in the amikacin group. Two of three patients treated with netilmicin and six of eight treated with amikacin responded.

Adverse reactions. In the netilmicin group, 19 of the 36 evaluable patients (52.8%) had 30 total adverse reactions, including nephrotoxic-

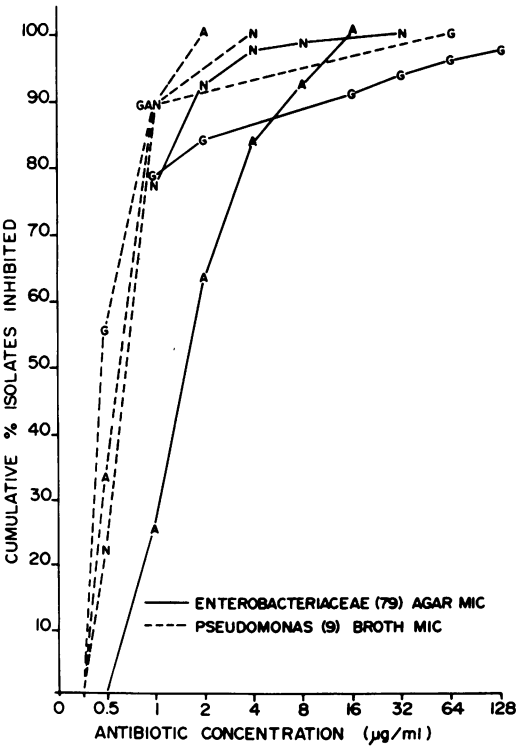

FIG. 1. *Cumulative percentage of inhibition of isolates by amikacin (A), gentamicin (G), and netilmicin (N).*

ity, ototoxicity, and other usually minor reactions of eosinophilia, drug fever, and change in liver function tests. In the amikacin group, 21 of 33 evaluable patients (63.6%) had 27 adverse reactions due to the drug (Tables 3–5).

Nephrotoxicity. Two patients treated with netilmicin were undergoing chronic dialysis, 34 others were evaluable, and 13 (38.2%) had nephrotoxicity (Table 3) leading to discontinuation of drug in 5. In six of the 13, nephrotoxicity was definitely due to the drug. In three of these, the rise was noted during therapy (on days 7, 22, and 39); in the other three patients, the rise was noted 6, 7, and 11 days after therapy. The mean rise of creatinine was 1.1 mg/100 ml (range, 0.6 to 2.8 mg/100 ml); the maximum value was noted after therapy in five patients. The mean duration of therapy before the rise in creatinine was 14.1 days (range, 6 to 41) in the definite group and 10.4 days (range, 5 to 23) in the possible and doubtful categories.

Possible nephrotoxicity due to drug was noted in four patients and was doubtful in three. These seven patients had received other potentially nephrotoxic antimicrobial agents with 7 days (including gentamicin, cephalosporins, or cotrimoxazole) or had shock, septicemia, dehydration, or congestive heart failure. The mean rise in serum creatinine in these seven patients was 1.4 mg/100 ml (range, 0.6 to 2.5 mg/100 ml). The mean rise in creatinine for all 13 patients with nephrotoxicity treated with netilmicin was 1.3 mg/100 ml (range, 0.6 to 2.8 mg/100 ml). Mean serum creatinine concentrations 1 month after therapy in 11 patients (two had expired) were 1.5 times the base-line level (range 0.9 to 2.4).

Four patients in the amikacin group were undergoing chronic dialysis; of the 29 evaluable patients, eight (27.6%) had nephrotoxicity ($P > 0.10$ versus netilmicin group). Rise in creatinine definitely due to the drug occurred in one patient ($P > 0.10$ versus netilmicin group). Possible

TABLE 3. *Nephrotoxicity in 34 patients treated with netilmcin and 29 treated with amikacin*

Nephrotoxicity	Netilmicin	Amikacin
Definite	6 (17.6)[a]	1 (3.4)
Possible	4 (11.8)	2 (6.9)
Doubtful	3 (8.8)	5 (17.2)
Total	13 (38.2)	8 (27.6)

[a] Numbers in parentheses are percentages.

TABLE 4. *Ototoxicity in patients treated with netilmicin and amikacin*

Toxicity to the cochlea	Netilmicin		Amikacin	
	No.	%	No.	%
Audiogram changes				
Definite	1/29[a]	3.4	6/23	26.1
Possible	1/29	3.4	0	0
Total	2/29	6.8	6/23	26.1
Tinnitus only	1/34[b]	2.9	1/29	3.4
Total cochlear toxicity	3/34	8.8	7/29	24.1
Vestibular toxicity (nystagmus)	1/34[c]	2.9	0/29	0

[a] Number who had audiogram changes/number who had serial audiograms.
[b] Number who had tinnitus only/number of responsive patients questioned for tinnitus.
[c] Number who had nystagmus/number evaluable by bedside testing.

TABLE 5. *Miscellaneous adverse reactions*

Reaction	No. showing reaction	
	Netilmicin ($n = 36$)	Amikacin ($n = 33$)
Change in liver function tests		
Definite	2	0
Possible	2	4
Doubtful	2	5
Total	6 (16.7)[a]	9 (27.3)
Drug fever, definite	2 (5.6)	0
Eosinophilia		
Definite	4	2
Doubtful	0	1
Total	4 (11.1)	3 (9.1)
Leukemoid reaction, definite	1 (2.8)	0
Hematological reactions (total)	5 (13.9)	3 (9.1)

[a] Numbers in parentheses are percentages.

nephrotoxicity was noted in two patients, and doubtful nephrotoxicity was noted in five. The mean rise in serum creatinine in these seven patients was 0.7 mg/100 ml (range, 0.5 to 1.6 mg/100 ml). The duration of therapy before the rise was 11.5 days (range, 4 to 20 days) in the possible and doubtful categories; for all patients it was 10.4 days (range, 4 to 20). The mean rise in creatinine for all eight nephrotoxic patients in the amikacin group was 0.7 mg/100 ml (range, 0.5 to 1.6 mg/100 ml). Serum creatinine concentrations could be obtained at 1 month in only three patients and were 0.7, 1.0, and 1.2 times the base-line level; the other five patients had expired.

Factors which were non-contributory to nephrotoxicity in a comparison of toxic and nontoxic patients in the treatment groups and both groups were: age, days of therapy, total dose, valley levels, severity of illness, presence of diabetes, bacteremia, increasing peaks during therapy, increasing valleys during therapy, diuretic administration (remote and recent), aminoglycoside administration (remote and recent), and hemodialysis.

The significant risk factors appeared to be different for each drug. The pretherapy creatinine levels in nephrotoxic patients receiving amikacin were greater than in the nontoxic amikacin patients ($P = 0.01$). Risk factors for patients receiving netilmicin were: elevated peak levels ($0.025 > P > 0.01$) and high pretherapy creatinine levels ($0.10 > P > 0.05$). A significantly greater number of patients in the amikacin group had shock ($0.05 > P > 0.02$) than in the same group receiving netilmicin. However, there was no relationship between shock and nephrotoxicity in either group ($P > 0.10$).

Ototoxicity. Twenty-nine patients who received netilmicin had serial audiograms. Three exhibited cochlear toxicity (Table 4). Two had significant changes in the audiogram at high frequency; neither had noticeable loss in the conversational range. One patient with endocarditis had definite ototoxicity. Tinnitus and a unilateral loss of 20 decibels at 8,000 Hz were noted on the 26th and 27th days of therapy. The netilmicin was discontinued, and 4 days later the audiogram reverted to base-line. The mean peak and valley serum levels were, respectively, 6.3 and 1.0 μg/ml. Another patient had a unilateral 20-decibel loss at 8,000 Hz after 5 days of netilmicin, but had received one dose of gentamicin 24 h before netilmicin (the gentamicin level drawn immediately before the netilmicin level was 1.0 μg/ml), and the loss could not be definitely attributed to netilmicin. The mean peak and valley serum levels were, respectively, 21.5 and 16.8 μg/ml. The audiogram returned to base line 12 days after therapy. One patient had tinnitus without audiogram changes which necessitated stopping the drug on the 5th day of therapy. One patient developed nystagmus due to netilmicin which resolved when the drug was stopped; he did not have vertigo. Therefore, four patients had manifestations of toxicity to one portion of the eighth nerve during netilmicin therapy.

Six of the 23 patients who received amikacin and had serial audiograms had high-frequency hearing loss definitely due to amikacin ($P > 0.10$ versus netilmicin); one other patient had tinnitus only. No patient had conversational loss. Two of the six patients who had audiogram changes were undergoing chronic dialysis; hearing loss was not reversible in these two patients. Repeat audiograms obtained 6 days, 2 weeks, and 2 months after therapy in three patients revealed that the hearing had returned to base line. The sixth patient was lost to follow-up. No patient had nystagmus or vertigo. There was no clear difference in total cochlear toxicity ($P > 0.10$) or in toxicity to the entire eighth nerve ($P > 0.10$) between the two groups.

Ototoxic amikacin patients received more days of therapy than the nontoxic group ($0.10 > P > 0.05$) and received more drug ($0.025 > P > 0.01$). Ototoxic netilmicin patients had higher peak levels than the nontoxic group ($0.01 > P > 0.005$) and higher valley levels ($0.01 > P > 0.005$). All ototoxic netilmicin patients were also nephrotoxic, whereas none in the ototoxic amikacin group was ($0.02 > P > 0.01$).

Miscellaneous. Twelve patients in the amikacin group and 13 in the netilmicin group had minor adverse reactions (Table 5). The only possible clinically significant adverse reaction was a transient leukemoid reaction, confirmed by bone marrow examination, which resolved shortly after netilmicin therapy.

DISCUSSION

An aminoglycoside is usually required for initial therapy of nosocomial suspected or known gram-negative bacillary infection. Two factors to consider are the risk of adverse reactions and the high prevalence of resistance to gentamicin noted in some institutions (18–20, 23). Gentamicin and amikacin have been equally effective with susceptible pathogens and with no differences in toxicity in a double-blind study (27), but amikacin is considered for initial therapy where there is a significant risk of gentamicin resistance (18–20). Although active in vitro against many gentamicin-resistant bacilli, netilmicin is less active than amikacin against gentamicin-resistant *P. aeruginosa* and *P. stuartii* (4, 17).

Our in vitro data for pretherapy organisms (Fig. 1) confirm the activity of netilmicin and amikacin against *Pseudomonas* and *Enterobacteriaceae*, including those which are resistant to gentamicin. Four patients in the netilmicin group, however, had pathogens resistant to netilmicin but susceptible to amikacin. Development of resistance to netilmicin during therapy, noted here in four instances, was also found in four patients in another study (29). The narrower spectrum of netilmicin compared with amikacin, particularly for many gentamicin-resistant organisms, may limit the use of netilmicin in initial therapy of serious nosocomial infections before susceptibility data are available.

The pharmacology of netilmicin is similar to that of gentamicin (9, 14, 25), but the alpha phase of netilmicin is more rapid than that of gentamicin (27), and higher doses (2 mg/kg per 8 h) have been recommended to achieve equivalent serum levels (9). Initial serum levels were predictable in only a small majority of our patients, although levels were less variable than gentamicin in another study (26). Mean peak serum levels were similar to those previously reported using comparable doses (16, 22, 29, 30), although some investigators (16, 29) did not adjust initial doses for reduced creatinine clearances. Because initial levels may be unpredictable, peak and valley levels should be obtained early in netilmicin therapy, as with other aminoglycosides. Amikacin levels were more predictable, however, in this study.

Both netilmicin and amikacin were effective for most infections in our study. The higher proportion of genitourinary tract infections or greater mean age in the netilmicin group and the greater severity of infections in the amikacin group (Tables 1 and 2) make it difficult to conclude from our data that the two drugs are equally efficacious. However, comparable in vitro data and response to treatment suggest that these two aminoglycosides have similar efficacy with susceptible pathogens. Response rates to both drugs were similar to those noted previously (2, 5, 11, 12, 16, 18, 29, 30). Most of the patients who had infections with gentamicin-resistant pathogens responded, but the small number of patients makes comparison between the two drugs difficult. Suprainfections were more common in our patients treated with netilmicin and, in a previous comparative study of urinary tract infections, were more common with amikacin therapy (16).

Therapeutic failures in our study were generally due to severe infection; the mean peak serum levels for these patients did not differ from the levels in the patients who responded. Additional reasons for three of the four patient failures in the netilmicin group were inability to achieve satisfactory levels in the biliary tract, development of netilmicin resistance during therapy, and endocarditis on a prosthetic valve. Factors which contributed to the seven failures in the amikacin group included extensive infection in five, urosepsis with an indwelling Foley catheter in one, and discontinuation of the drug due to nephrotoxicity in one.

In some clinical studies netilmicin has been associated with a low incidence of nephrotoxicity (11, 16). Other investigators who used doses of netilmicin comparable to those used our study noted significant nephrotoxicity rates from 14 to 26% (2, 5, 11, 12, 22, 29, 30). In our study netilmicin was definitely associated with nephrotoxicity in more patients (17.6%) than amikacin (3.4%), although the difference was not statistically significant. Precise comparison with all previous studies is not possible because the same strict criteria for definite nephrotoxicity have not always been used. There was no significant difference between netilmicin (38.2%) and amikacin (27.6%) for nephrotoxicity when all patients were considered. However, mean rise in serum creatinine was greater for all nephrotoxic patients treated with netilmicin (1.3 mg/100 ml) than with amikacin (0.7 mg/100 ml). Age was not related to development of nephrotoxicity for either antibiotic; this observation agrees with previous studies (5, 28). Of concern is the possibly persistent nature of nephrotoxicity seen with netilmicin; the 1-month follow-up creatinine fell to <1.25 times the base line in only three patients. Five of the eight patients with amikacin nephrotoxicity expired, but the three surviving patients demonstrated reversible nephrotoxicity.

The low incidence of cochlear toxicity due to netilmicin (2, 5, 11, 16, 22, 29) is confirmed by our study. Hearing loss was reversible within a few days in the two patients in our study who had audiogram changes, although some patients have had irreversible loss due to netilmicin (30). Audiogram changes were more frequent in our patients treated with amikacin than reported in some previous studies (18, 19, 27) but two of our six patients had chronic renal failure which may have led to high serum levels between dialysis and hearing loss. Nystagmus was noted only in one patient who received netilmicin and in none who received amikacin. Netilmicin was associated with less cochlear toxicity than amikacin, but caloric testing, cochlear nerve conduction studies, and electronystagmometry were not done.

Changes in liver function tests and other minor adverse reactions have been noted in previous netilmicin clinical trials (2, 5, 22, 29). In all

our patients who received netilmicin or amikacin, the changes were transient and of no known import.

Amikacin appears to be the initial drug of choice in therapy of serious infections caused by gram-negative bacilli documented or suspected to be resistant to gentamicin; however, the effectiveness of netilmicin against pathogens susceptible in vitro and the relatively low incidence of high-frequency changes in audiograms indicate that it has a role in therapy, particularly in patients with impaired hearing or at risk for hearing loss. The finding of nephrotoxicity with netilmicin despite monitoring of serum levels indicates that animal models probably do not correlate with clinical experience. Double-blind clinical trials, including those with large numbers of patients and using sophisticated tests of vestibular function, are necessary to define the exact role of both agents, which appear equally efficacious with susceptible pathogens.

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