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Netilmicin: Clinical Efficacy, Tolerance, and Toxicity

ANAND P. PANWALKER,* JAMES B. MALOW, VICTORIA M. ZIMELIS, AND GEORGE G. JACKSON

University of Illinois Hospital and the Section of Infectious Diseases, Department of Medicine, Abraham Lincoln School of Medicine, University of Illinois College of Medicine, Chicago, Illinois 60680

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Netilmicin, a new aminoglycoside antibiotic, has increased in vitro bactericidal activity against many strains of *Enterobacteriaceae* as compared to other aminoglycosides. It is a poor substrate for some of the common gentamicin-inactivating enzymes, and it has minimal toxicity in experimental animals. In 27 hospitalized patients, clinical cure was achieved in all, and the initial infecting organism persisted in only one. Therapeutic serum and urine levels were easily obtained in most patients. No ototoxicity was observed in two patients whose treatment required inordinately high serum levels and in whom other risk factors were present. Ototoxicity in 1 of 21 patients studied was unilateral, partially reversible, and not associated with high serum levels. Although nephrotoxicity occurred in 4 of 25 patients (16%), other host factors could have accounted for the toxicity in two patients. A new observation, not noted with other aminoglycoside antibiotics, was the elevation of serum alkaline phosphatase in 43% of the patients studied.

Serious infections caused by aerobic gram-negative bacilli continue to be a major cause of morbidity and mortality of hospital patients. Their treatment is one of the principal indications for the use of aminoglycoside antibiotics. A new aminoglycoside antibiotic, netilmicin, is a member of the gentamicin family of drugs. Chemically, it is 1-*N*-ethyl sisomicin, an analog of gentamicin C_{1a}. Theoretical advantages of netilmicin are threefold: (i) an increased in vitro bactericidal activity over gentamicin against many strains of *Enterobacteriaceae* (1-3, 5, 6, 10, 11, 13, 15-17, 20, 22, 23); (ii) the inhibition of gentamicin-resistant strains when the resistance is associated with one of the gentamicin-inactivating acetylases (aminoglycoside acetylase-3i, -ii, or -iii) or an adenylase (aminoglycoside nucleotidylase-2″), which have been common modes of resistance among *Enterobacter* species, *Escherichia coli,* and *Pseudomonas aeruginosa* (4, 16, 18); (iii) relative freedom from ototoxicity and reduced nephrotoxicity in experimental animals (12, 20). Also, there is a suggestion that the serum levels may be more predictable than those of gentamicin (19). These favorable features of netilmicin suggest the possibility of more effective therapy of serious gram-negative bacterial infections with diminished drug toxicity and formed the basis for the investigations reported here.

MATERIALS AND METHODS

Thirty-one patients on the Medical and Surgical Services of the University of Illinois Hospital entered the study. Four patients who received netilmicin for less than 48 h were excluded, two had nonbacterial "chemical" peritonitis, one died of sepsis after a single injection of netilmicin, and one withdrew from the study. The age distribution of the remaining 27 patients was 16 to 85 years (mean, 43). There were 18 females and 9 males. The underlying diseases were: hemoproliferative malignancy, 2; cirrhosis and hepatitis, 7; paraplegia, 3; renal transplantation, 3; chronic renal failure, 1; uretero-ileal conduit after resection of bladder carcinoma, 3; diabetes mellitus, 1; and sickle thalassemia, 1. The condition of the patients was critical in five, serious in six, and fair to good in the remainder. Other appropriate antibiotics were used concomitantly in four patients. Fever, chills, hypotension, or all three were associated with bacteremia. Urinary tract infections were diagnosed on the basis of characteristic signs, symptoms, and bacteriuria (>100,000/ml) in midstream or catheter specimens. Three patients with the classical clinical syndrome of acute pyelonephritis and pyuria were included, although no significant bacteriuria was demonstrated. Localization procedures such as intravenous pyelograms and fluorescent staining for antibody-coated bacteria were performed in most patients with urinary tract infections. Patients with pneumonia had fever, sputum production, new pulmonary infiltrates on chest roentgenograms, and persistent isolation of the same organism from sputum. Clinical features, repeated isolation of the same gram-negative organisms

from wounds and surgical specimens, and classical radiological signs were the criteria for the diagnosis of soft-tissue infections and osteomyelitis.

Dosage. After informed consent was obtained, initial treatment was started at 4.5, 6.0, or 7.5 mg/kg per day in divided doses at 8-h intervals; the higher dosage schedules were used in severely ill patients. Alterations in treatment were based on serum antibiotic levels and serum creatinines. Eight patients who had thrombocytopenia, shock, or severe illness received intravenous therapy; the remainder received intramuscular injections.

Monitoring toxicity. Routine laboratory studies performed before, during, and after therapy included a complete hemogram, urine analysis, serum glutamic oxalacetic transaminase (SGOT), alkaline phosphatase, serum creatinine, blood sugar, and serum electrolytes. Where possible, creatinine clearances were measured. In patients with urinary tract infection, quantitative pyuria was measured (normal, <25,000 leukocytes/ml). Audiograms were done before or within 24 h of treatment in 21 patients and again after treatment. When possible, tests were done in a soundproof room with an Audiotone Royal audiometer (Division Industries, Phoenix, Ariz., model AUI-SP 3066). In lieu of caloric testing, patients were questioned and observed regarding the development of tinnitus, dizziness, or ataxia.

Ototoxicity was defined as a mean decrease of greater than 10 decibels in auditory acuity in the range of 250 to 8,000 Hz and/or a decrease of at least 15 decibels in two or more frequencies in either ear. Nephrotoxicity was defined as an increase in serum creatinine of 0.4 mg/dl or greater, if the initial serum creatinine was less than 2.0 mg/dl, or an increase of 0.8 mg/dl or greater, if the initial creatinine was greater than 2.0 mg/dl. Nephrotoxicity was "definite" if no other causes of renal insufficiency (e.g., hypotension, dehydration, papillary necrosis, etc.) were found in the 72-h period before measured rise in serum creatinine. If another possible etiology existed to account for the rise in serum creatinine, it was termed "possible" nephrotoxicity.

Microbiological studies. Cultures of blood, urine, and other appropriate sites were obtained before, during, and after treatment and, in the case of urinary infections, at 2 and 4 weeks after completion of therapy. Species of bacteria were identified by routine methods in the clinical bacteriology laboratory. A serial tube dilution method with tryptose phosphate broth was used to determine the minimal inhibitory concentration (MIC) of netilmicin and gentamicin for most study strains, but for comparative purposes some strains were also studied using Mueller-Hinton broth.

Serum and urine levels. Peak and trough serum levels of netilmicin were measured frequently during treatment with the agar well diffusion method, using *Staphylococcus epidermidis* (ATCC 27626) as the indicator strain. On days 3 to 6 of treatment, an 8-h urine collection with periodic serum levels was obtained to study the excretion of netilmicin. Simultaneously, a creatinine clearance was measured.

Patient evaluation. Patients with bacteremia and/or severe tissue infections were considered bacteriologically and clinically cured if all signs and symptoms disappeared and the infecting organism was eradicated. For urinary tract infections, symptomatic improvement and elimination of infecting organisms for at least 4 weeks post-treatment was considered a cure. If there was superinfection, reinfection, or relapse, the cure was appropriately qualified.

RESULTS

Thirty-one patients received netilmicin. Of these, four received less than 48 h of treatment and were excluded from analysis. The susceptibility of the organisms recovered in the study and 130 other clinical isolates at the University Hospital are shown in Fig. 1. The MICs for the study strains measured in tryptose phosphate broth ranged from 1 to 32 μg/ml. The range of MICs for the other clinical isolates was 0.25 to 125 μg/ml, although the MIC did not exceed 8.0 μg/ml in most. For 26 strains tested in Mueller-Hinton broth, the MIC was two- to eightfold lower. A majority of peak serum levels exceeded the MIC of the organisms (in tryptose phosphate broth), and the urinary concentrations of the drug were always above the MIC. In patients with a serum creatinine value <2.0 mg/dl who received intramuscular injections, there was a stepwise increment in peak (1 h postdose) and trough (8 h postdose) serum levels for three rising dosage schedules of 4.5, 6.0, and 7.5 mg/kg per day (Fig. 2). A majority of the peak levels in each dosage category were in the "desirable" (4 to 8 μg/ml) range (Fig. 3). Urine excretion of netilmicin measured during the 8-h interval between doses was a direct function of creatinine clearance. Patients with creatinine clearance above 50 ml/min excreted 80 to 100% of the dose given. Patients with decreased creatinine clearances of 30 to 50 ml/min had proportion-

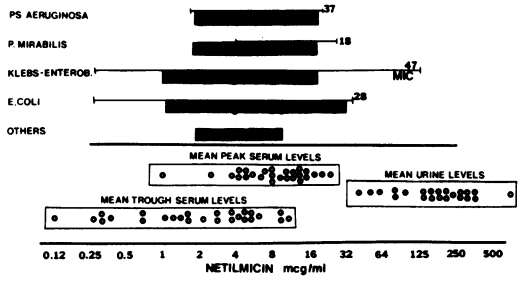

FIG. 1. *Relation of in vitro susceptibilities to mean peak and trough serum levels and mean urine levels. Dots within the shaded areas represent MICs of individual isolates from study patients. The range of MICs of other clinical laboratory isolates is represented by the bars. The numbers alongside the bars indicate the number of clinical laboratory strains tested.*

ately decreased netilmicin urine excretion of 30 to 80%. There was no measurement of netilmicin excretion in patients with creatinine clearances of less than 30 ml/min.

The results of treatment are shown in Table 1. The patients are categorized according to the presence of bacteremia, tissue infection, or urinary tract infection.

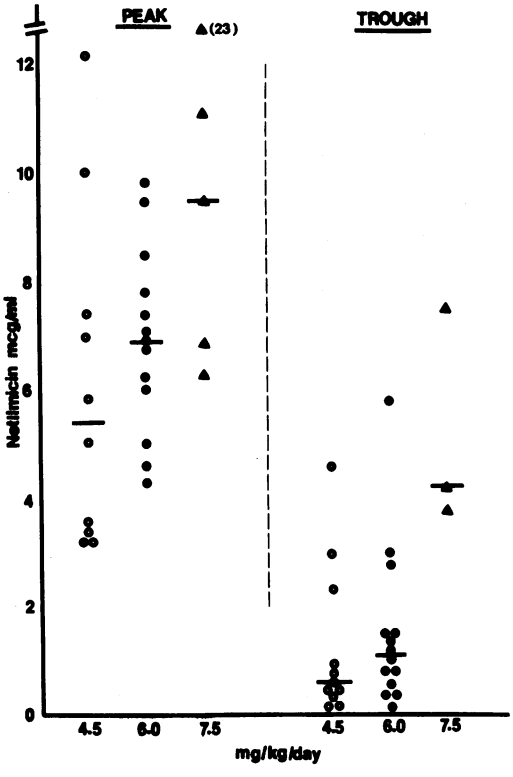

FIG. 2. *Peak and trough serum levels achieved in patients with serum creatinines less than 2.0 mg/dl receiving netilmicin doses of 4.5, 6.0, or 7.5 mg/kg per day intramuscularly. The bars indicate median serum levels at each defined dose.*

Bacteremia. Excluding one patient with *Bacteroides fragilis* bacteremia (discussed below), 9 of the 27 patients had bacteremic disease. Five had gram-negative rod bacteremia from a urinary portal, one had streptococcal endocarditis, one had disseminated gonococcemia, and the source of gram-negative rod sepsis was indeterminate in the remaining two patients. All bacteremic patients were clinically and bacteriologically cured. Although netilmicin may have been synergistic with penicillin in the patient with streptococcal endocarditis, it is possible that penicillin may have cured the infection alone.

Illustrative cases. (i) Bacteremia with gram-negative bacilli. (a) LM. A 38-year-old patient with chronic myelogenous leukemia had had klebsiella bacteremia intermittently for 6

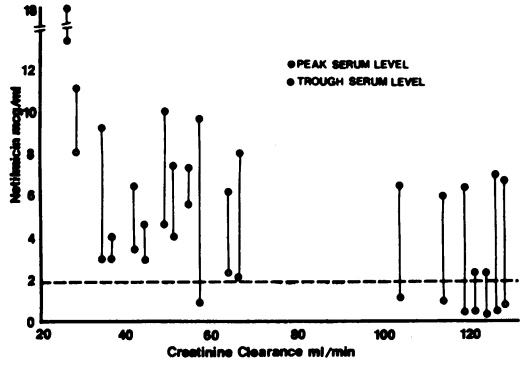

FIG. 3. *Maintenance (more than 3 days) peak and trough serum levels compared to simultaneous creatinine clearances. Vertical bars connect peak and trough serum levels of individual patients.*

TABLE 1. *Site of infection and bacteriological response to treatment*

Etiology	Bacteremia		Tissue infections[a]		Urinary tract infections[b]		
					Eradication of initial strain		Failure or relapse
	Cure	Failure	Cure	Failure	Cure 4 wks post-treatment	New infection	
E. coli	4	0	1	1	4	0	0
Klebsiella-Enterobacter	2	0	2	0	7	3	0
P. mirabilis	1	0	1	0	2	1	0
Pseudomonas			1	0	2	0	0
Other	2	0					

[a] Six isolates were obtained from four patients: *E. coli* and *Klebsiella* and *Klebsiella* and *P. mirabilis* were present in two of the patients.

[b] Fifteen pretreatment isolates were obtained from 12 patients (*P. mirabilis* and *P. aeruginosa, E. coli* and *Klebsiella,* and *E. cloacae* and *E. coli* were obtained from three of these patients). Superinfections or reinfections were caused by *Candida* species (two patients), *P. rettgeri,* and *Pseudomonas maltophilia* (one patient each).

months with relapses following gentamicin/cephalothin treatment. Bacteremia was eradicated by netilmicin treatment and the patient improved clinically. However, a lung infiltrate and pleural effusion developed while the patient was receiving netilmicin. It subsided during subsequent treatment with chloramphenicol.

(b) RS. Shock and enterobacter bacteremia, without an identifiable portal of entry, occurred in a 52-year-old female in the hospital because of a myocardial infarction. There were multiple episodes of arrhythmias, and the patient required mechanical ventilation. After treatment with netilmicin, her condition improved rapidly, with clearing of the bacteremia, and she was discharged.

(ii) Disseminated gonococcemia: DV. A 22-year-old female, with chronic idiopathic liver disease and penicillin allergy, presented with a clinical picture of gram-negative sepsis, which included fever, chills, and hypotension. After 5 days of netilmicin therapy, the initial blood cultures grew *Neisseria gonorrhoeae*. Significant clinical improvement had already occurred, and the infection was eradicated after 2 weeks of netilmicin.

Tissue infections. Six organisms were isolated from four patients with severe tissue infections.

(i) Pneumonia. Two patients with pneumonia were cured. One with *E. coli* pneumonia received concomitant ampicillin therapy. In spite of clinical cure, the *E. coli* persisted in the sputum cultured after completion of therapy.

(ii) Wound infection. One patient had a severe abdominal wall wound infection after renal transplantation. A gentamicin-resistant strain of *P. aeruginosa* (MIC >500 μg/ml) was recovered in pure culture; the isolate was susceptible to 16 μg of netilmicin per ml. The organism was eliminated from the wound within 72 h; however, because of persistent fever, carbenicillin (which in vitro was synergistic with netilmicin) was added. Resolution of fever occurred in 3 weeks with combined therapy.

(iii) Osteomyelitis. A patient with osteomyelitis of the right hip and acetabulum had severe soft-tissue infection in the gluteal region secondary to deep infected decubiti and bacteremia with *B. fragilis. Proteus mirabilis* and klebsiella were isolated repeatedly from the wounds and surgically excised bone. The patient received treatment with netilmicin and clindamycin for 6 weeks. Clinical improvement and a bacteriological cure were attained, but a netilmicin-resistant strain of *Acinetobacter calcoaceticus* var. *anitratus* (MIC, 500 μg/ml) colonized the healing wound.

Nonbacteremic urinary tract infections. Fifteen organisms were isolated from the urine cultures of 12 patients. Ten of the 12 patients had a febrile illness; 2 others who were asymptomatic had infected renal allografts. In one of the latter, the infection was caused by a gentamicin-resistant strain of *Enterobacter cloacae*. Fluorescent stains for the demonstration of antibody-coated bacteria in urine were positive in six of the eight patients studied. Treatment with netilmicin eradicated the infecting strains in all patients, and no relapses had occurred 4 weeks after the completion of treatment. During this period there were two superinfections with strains of yeast and two bacterial reinfections. Three patients with a clinical diagnosis of acute pyelonephritis are not shown in Table 1. The symptoms in these patients disappeared during treatment.

Ototoxicity. Only one patient complained of tinnitus with dizziness, which was transient and not associated with ataxia, nystagmus, or audiometric changes. Of 21 patients who had audiometric studies, one had ototoxicity. As shown by audiometry, this was partially reversible and did not involve hearing loss of tones in the conversational range. The patient was 42 years old, had paraplegia, and was treated with both netilmicin and clindamycin for bacteremia with shock. The treatment lasted 42 days and was not associated with high peak levels of netilmicin (range, 5.8 to 8.3 μg/ml), although the trough levels rose from 2.4 μg/ml on day 4 (on 7.5 mg/kg per day) to 4.9 μg/ml on day 30 (on 4.5 mg/kg per day). There was no history of previous aminoglycoside or diuretic treatment.

The absence of ototoxicity in two of the patients is notable. One, who was undergoing hemodialysis, developed peak levels as high as 36 μg/ml (range, 15 to 36 μg/ml) and trough levels as high as 24 μg/ml (range, 10 to 24 μg/ml) over a treatment period of 3 weeks. These high levels were deemed necessary for cure in an immunosuppressed patient with a moderately resistant organism. No evidence of toxicity appeared in the audiogram performed on day 16 of treatment. Another patient, who developed nephrotoxicity, had high peak and trough levels, prolonged treatment, and previously documented gentamicin-related hearing loss. No worsening of the initially abnormal audiogram was demonstrated.

Nephrotoxicity. Twenty-five patients had either serum creatinine or creatinine clearance data adequate for analysis of nephrotoxicity. By previously defined criteria, 4 of 25 patients (16%) had significant changes in renal function during therapy. In two of these patients the elevation in serum creatinine was evaluated as probably related to the drug therapy (definite

toxicity) and in the other two patients as possible drug-related toxicity. Two patients with toxicity were male (from a total of seven) and two were female (from a total of 18). Three of the four patients were bacteremic, but none were in shock at any time. Three of the four patients had underlying renal disease (urethral stricture, papillary necrosis, and/or pyelonephritis), and two had received other aminoglycosides within the past year. Although not statistically significant, the patients with nephrotoxicity in comparison to nontoxic patients were older, received treatment for longer periods of time, and received a larger total amount of netilmicin, but the mean daily dose was not different in the two groups. There were no differences in peak or trough serum levels achieved in the first 72 h. In the maintenance period, however, both the peak and trough levels were higher in the toxic patients ($P = 0.002$ and 0.047, respectively). The elevations in serum creatinine were noted during days 3 to 5 of therapy in two of the patients, and the elevated serum levels could have been either secondary to worsening renal function or a cause for the toxicity. One patient developed toxicity after 4 weeks of treatment when the dose of netilmicin was increased. The toxicity was transient in all patients, with serum creatinine returning to pretreatment levels soon after discontinuation of therapy.

Elevations of alkaline phosphatase. Nine of 21 patients (43%) who had serial measurements of SGOT and alkaline phosphatase adequate for analysis had an increase in serum alkaline phosphatase ranging from 23 to 209% as compared to their initial measurement, attaining pathological levels in all but one. However, there was no clinical evidence of hepatobiliary toxicity. No sequelae or persistent abnormalities were recognized after the treatment was stopped. In five of six patients with electrophoretic fractionation of the serum alkaline phosphatase, the liver band was the predominant one and was increased above normal. In the remaining patient, bands characteristic of both intestinal and liver alkaline phosphatase were present. Elevations of SGOT accompanied the rise in alkaline phosphatase in three of the nine patients and were also seen in two patients with no rise. Underlying liver disease (cirrhosis, hepatitis) was unrelated to enzyme elevations, being present in three patients with alkaline phosphatase rise and four patients showing no rise. Three of the four nephrotoxic patients also developed a significant elevation of alkaline phosphatase. The patients with drug-related elevations of alkaline phosphatase were older, had a longer duration of therapy, and received a higher total and mean daily dose; however, none of these differences were statistically significant. Mean peak serum levels after 3 days were significantly higher ($P = 0.02$) in patients with elevated alkaline phosphatase than in the others; trough levels were also increased, but the difference was not significant ($P = 0.2$). After exclusion of the nephrotoxic patients, peak and trough serum levels after day 3 remained higher for the group with elevated alkaline phosphatase.

DISCUSSION

Factors that dictate the choice of an aminoglycoside antibiotic include favorable clinical and experimental therapeutic experience, the spectrum of antibacterial activity, prevalence of resistant strains, and the toxicity of the drug. The therapeutic results obtained in this investigation are remarkably good. Nearly all of the infections were cured, although the underlying diseases were serious in many of the patients. In the four instances where other antibiotics were used in conjunction with netilmicin, synergy was either demonstrated or expected. In these patients, cure cannot be attributed to netilmicin alone. In a controlled study, the therapeutic efficacy of gentamicin and amikacin approached 80% (21). Thus, the efficacy of netilmicin appears to be at least as good as that with other effective aminoglycoside antibiotics.

The increased in vitro activity of netilmicin can be considered to increase its therapeutic potential, but this advantage, if any, cannot be evaluated in this trial. Two of the isolates from patients in the series were resistant to gentamicin and susceptible to netilmicin. Thus, the ability of netilmicin to withstand inactivation by some of the most common bacterial enzymes associated with gentamicin-resistant strains broadens its base of activity, although not as completely in this respect as amikacin (4, 16). This property should decrease the ease with which resistant strains can emerge during the selective pressure of antibiotic administration to patients.

A principal limiting factor in the treatment of serious gram-negative bacterial infections with aminoglycoside antibiotics is the narrow ratio between therapeutic and toxic serum levels. Peak serum concentrations of gentamicin below 4 μg/ml have been associated with persistent bacteremia with *P. aeruginosa*, causing a greater fatality rate than when higher drug levels were achieved (9). Peak postinjection levels of gentamicin above 8 μg/ml produce an increased risk of ototoxicity and possibly also nephrotoxicity (8). A dose of 6 mg of netilmi-

cin/kg per day produced peak serum levels above 4 and below 10 μg/ml, with a median level of 7 and a trough level less than 2 μg/ml in all but a few patients. This may be ideal for the treatment of serious infections other than those of the urinary tract, which may not require such high plasma levels.

The almost complete freedom from ototoxicity after netilmicin administration to animals is important, if it can be confirmed in humans (20). Of particular interest is the absence of any discernible ototoxicity in two patients who developed extraordinarily high serum levels of netilmicin for periods of 2 to 3 weeks. On the other hand, the partially reversible unilateral ototoxicity found in one patient with usual therapeutic levels indicates that ototoxicity occurring in the course of treatment of serious illness and combination with other drugs is not entirely predictable and not related only to the plasma concentration of drug.

Nephrotoxicity was considered definitely related to netilmicin in two patients (8%) and possibly drug related in two others. This is comparable to the rate of toxicity noted with amikacin (17%) (14) and gentamicin (2 to 10%) (7). Thus, the animal data showing netilmicin to be far less nephrotoxic than gentamicin and amikacin are not confirmed in this investigation. Perhaps the animal studies are not relevant to humans, but more likely is the greater importance of other factors that may predispose patients to drug-induced renal damage. As in previous experience, the host factors found to be of particular importance in the development of nephrotoxicity were prior aminoglycoside therapy, increased age, and underlying renal disease and, among the drug factors, higher serum levels, longer duration of therapy, and a larger total dose.

A significant rise in hepatic enzymes has not been recognized with most of the aminoglycoside antibiotics. In this experience, however, elevation of serum alkaline phosphatase occurred in 43% of the patients tested and was of hepatic origin in all patients whose sera were fractionated. Failure of the level of SGOT to increase in parallel with the alkaline phosphatase might suggest the abnormality is in the biliary ducts, rather than the liver parenchyma. Three of the nine patients with elevated levels of alkaline phosphatase also had nephrotoxicity; thus, the effect may have factors in common. Patients with enzyme rise were older, received a higher dose of netilmicin, and had higher trough serum levels; however, none of these were statistically significant. The peak serum level of drug measured after 3 days of therapy was consistently higher ($P = 0.02$). This further relates the alteration directly to netilmicin treatment, but since no sequelae or persistent abnormalities were recognized, its importance is unknown.

Results of this study show that netilmicin is an effective antibiotic. The advantages of increased bactericidal activity and reduced risk of ototoxicity with prolonged therapy and high levels recommend it as an improvement over gentamicin in the treatment of severe gram-negative bacterial infections. Nevertheless, the potential for ototoxicity and nephrotoxicity remains appreciable. In addition, the association of netilmicin in the production of increased serum levels of alkaline phosphatase in a high proportion of patients is a new finding that requires further evaluation.

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