Clinical efficacy and toxicity of netilmicin in the treatment of gram-negative infections

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Netilmicin, a new semisynthetic aminoglycoside antibiotic, was used to treat 41 infections in 38 patients. The outcome of four infections could not be evaluated: two patients received inadequate therapy and two did not have gram-negative infections. Clinical improvement occurred in 36 (97%) of the 37 gram-negative infections, and bacteriologic cure occurred in 30 (86%) of the 35 evaluable infections. Therapeutic serum concentrations of netilmicin were readily achieved by both intramuscular and intravenous routes. Reversible ototoxic effects occurred in 1 (3%) of 35 courses of therapy evaluated, reversible nephrotoxic effects occurred in 5 (14%) of 36 courses and mild reversible alterations in liver function occurred in 3 (19%) of 34 courses. Netilmicin appears to be effective and safe in the treatment of aerobic gram-negative infections.

La nétilmicine, un nouvel antibiotique aminoglycoside semisynthétique, a été utilisée dans le traitement de 41 infections survenant chez 38 patients. Le résultat de quatre infections n'a pu être évalué: deux patients ont reçu un traitement insuffisant et deux ne souffraient pas d'infections gram négatif. Une amélioration clinique est survenue dans 36 (97%) des 37 infections gram négatif, et une guérison bactériologique est survenue dans 30 (86%) des 35 infections évaluables. Des concentrations sériques thérapeutiques de la nétilmicine ont été facilement atteintes par voie intramusculaire aussi bien que par voie intraveineuse. Des effets ototoxiques réversibles sont apparus dans 1 (3%) des 35 traitements évalués, des effets néphrotoxiques réversibles sont apparus dans 5 (14%) de 36 traitements, et des atteintes bénignes et réversibles de la fonction hépatique sont apparues dans 3 (19%) de 34 traitements. La nétilmicine semble être efficace et sûre dans le traitement des infections à bactéries aérobies gram négatif.

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Netilmicin is a new semisynthetic aminoglycoside antibiotic derived by ethylation of the 1-N position of the deoxystreptamine ring of sisomicin. It is effective in vitro against aerobic gram-negative bacteria, including some strains resistant to gentamicin and tobramycin.[2-6] Toxicity studies in animals have indicated that netilmicin is significantly less ototoxic and nephrotoxic than gentamicin.[5,7-9] This paper reports the results of an open study of the clinical efficacy and toxicity of netilmicin in the treatment of 41 infections, 39 due to aerobic gram-negative organisms, in 38 patients.

Methods and patients

Methods

After informed consent was obtained, hospitalized patients with proven or suspected infection due to aerobic gram-negative bacilli were admitted to the study. Netilmicin was given intramuscularly or intravenously as a 30-minute infusion in a dose of 1 to 2 mg/kg of body weight every 8 hours. In patients with abnormal renal function the dosage was modified: the rule of eight times the serum creatinine concentration was used to determine the dosage interval,[10] and subsequent adjustments were made according to the serum netilmicin concentrations.

Urinary tract infection was defined as the presence of more than 100 000 organisms per millilitre of a midstream urine specimen, or more than 10 000 organisms per millilitre of a urine specimen obtained by catheterization. Patients with bacteriuria accompanied by costovertebral angle tenderness and signs of systemic illness such as fever were considered to have pyelonephritis. Patients with bacteriuria but not the other findings and with negative results of an antibody-coated bacteria test were considered to have cystitis. Other infections were identified when clinical signs of infection were present and aerobic gram-negative organisms were cultured.

Cultures of blood, urine and other appropriate material were done before, during and after treatment and, in the case of urinary tract infections, 2 and 6 weeks after completion of therapy. Bacteria were isolated and identified by routine methods in the clinical microbiology laboratory. Antimicrobial susceptibility was determined by a standardized disc diffusion technique.[11] Organisms were considered to be susceptible to netilmicin if the zone of inhibition surrounding a 10-μg disc was 15 mm or more in diameter.

All patients were monitored clinically for local reactions to infections and for subjective changes in function of the eighth cranial nerve. Serial audiograms were obtained with a model 9D Beltone audiometer (Beltone Electronics, Chicago), and each patient was examined by a member of the otolaryngology department. Hematologic and biochemical studies were done before, during and after therapy.

Serum netilimicin concentrations were measured frequently during treatment with the agar well diffusion method; a multiply resistant strain of *Staphylococcus epidermidis* (supplied by Dr. S.J. Seligman, Downstate Medical Center, Brooklyn, New York) or *Bacillus subtilis* (American Type Culture Collection 6633) was used as the indicator strain.[12] Blood was obtained immediately prior to netilmicin injection or infusion and 1, 2 and 4 hours after injection or the start of the infusion.

Netilmicin was considered to have

been ototoxic if there was an average decrease of more than 10 dB in auditory acuity in the range of 125 to 8000 Hz. It was considered to have been nephrotoxic if the serum creatinine concentration increased by more than 0.4 mg/dL when the initial value was less than 3.0 mg/dL, or more than 0.9 mg/dL when the initial value was more than 3.0 mg/dL.[13] Nephrotoxicity was considered "definite" if no other cause of renal insufficiency (e.g., hypotension, concurrent administration of another nephrotoxic drug or dehydration) was identifiable within 72 hours before the change in the serum creatinine concentration. If there was another possible reason for the rise in the serum creatinine value the nephrotoxicity was termed "possible".

Genitourinary tract infections were considered cured if there was symptomatic improvement and elimination of the infecting organisms for at least 6 weeks after the end of antimicrobial therapy. If there was relapse or reinfection the cure designation was appropriately qualified. Other infections were considered cured if all signs and symptoms disappeared, the infecting organism was eradicated, and the patient remained free of infection during the 6-week follow-up period.

Patients

Thirty-six patients with 39 gram-negative infections were treated. The duration of therapy ranged from 5 to 14 days for genitourinary tract infections and from 7 to 42 days for other infections. Two patients who did not have gram-negative infections were also treated and were included in the study for analysis of netilmicin's toxicity: one patient received netilmicin for 7 days because of suspected gram-negative sepsis, and the other received netilmicin for 39 days for its possible synergistic effect in the treatment of vertebral osteomyelitis due to *S. aureus*.

Twenty-one patients were treated for 23 acute genitourinary tract infections: 18 patients had acute pyelonephritis, 1 had cystitis and 2 had prostatitis. One patient with *Escherichia coli* pyelonephritis also had gonorrhea. One patient had two episodes of pyelonephritis more than a year apart. Fifteen patients were treated for 16 other local or systemic infections. One patient with *Enterobacter* sp. bacteremia also had a catheter-associated urinary tract infection caused by *Pseudomonas aeruginosa*. Except for three patients with *P. aeruginosa* osteomyelitis who also received carbenicillin, netilmicin was the only antibiotic effective against aerobic gram-negative bacilli that was given.

The 19 men and 19 women had a mean age of 50 years (range 17 to 88 years). Netilmicin was given intramuscularly to 24 patients and intravenously to 14 patients. In three patients with abnormal renal function the dosage was modified. Underlying diseases were present in 26 patients and consisted of trauma in 7, diabetes mellitus in 5, malignant disease in 4, chronic renal failure in 2, benign prostatic hypertrophy in 2, and alcoholism, cerebrovascular accident, multiple sclerosis, pancreatitis, paraplegia and renal tubular acidosis in 1 each. Eleven patients had undergone surgical procedures during this hospitalization prior to the development of infection.

Results

Efficacy

The clinical and bacteriologic responses to therapy are summarized in Table I. Eleven patients were treated for 12 episodes of acute uncomplicated pyelonephritis. *E. coli* was cultured from 10 patients and *Klebsiella* sp. was cultured from 1 patient. The other patient had classic symptoms and signs of acute pyelonephritis, including pyuria; however, no organisms could be cultured from the urine. Although bacteriologic response was not evaluable, the condition was clinically cured. Initial cure was followed within 6 weeks by reinfection with different organisms in four patients. The other seven patients remained free of infection for at least 6 weeks.

Seven patients had acute pyelonephritis complicated by abnormalities of the urinary tract; two were infected with *E. coli,* two with *Klebsiella* sp., two with *P. aeruginosa* and one with *E. coli* and *Proteus vulgaris*. One patient with a clinical cure was lost to follow-up. In a patient with a neurogenic bladder and an indwelling catheter the initial *E. coli* infection was cured but reinfection with *Streptococcus faecalis* occurred within 6 weeks of the end of netilmicin therapy. The other five patients remained free of infection throughout the follow-up period.

One patient with chronic renal failure and hypersensitivity to a number of drugs had symptomatic cystitis of 4 months' duration that was unresponsive to oral antimicrobial therapy. Significant quantities of *E. coli* and *Citrobacter* sp. were repeatedly cultured. Netilmicin therapy resulted in clinical and bacteriologic cure; however, reinfection with a new organism occurred 6 weeks after the

Table I—Clinical and bacteriologic response to netilmicin of 39 gram-negative infections in 36 patients

Infection	No. of patients	Clinical response		Bacteriologic response		
		Improved	Failed	Cured	Failed	Not evaluable
Acute pyelonephritis						
Uncomplicated	11	12‡	0	11	0	1
Complicated	7	7	0	6	0	1
Cystitis	2	2	0	2	0	0
Gonorrhea	1*	1	0	1	0	0
Acute prostatitis	2	2	0	1	1	0
Bacteremia	3†	3	0	3	0	0
Soft tissue infection (*Pseudomonas aeruginosa*)	3	3	0	1	2	0
Osteomyelitis	7	4	1	4	1	2
Pericholecystic abscess	1	1	0	0	1	0
Septic arthritis	1	1	0	1	0	0

*This patient had acute uncomplicated *Escherichia coli* pyelonephritis concurrently.
†One patient with *Enterobacter* sp. bacteremia had catheter-associated cystitis caused by *P. aeruginosa*
‡One patient had two episodes of pyelonephritis.

end of therapy. One patient with *Enterobacter* sp. bacteremia was also found to have a catheter-associated bladder infection caused by *P. aeruginosa*. Netilmicin therapy and catheter removal resulted in clinical and bacteriologic cure.

Two patients had acute symptomatic bacterial prostatitis. One patient's infection was due to *E. coli* and was cured by a 7-day course of netilmicin. The other patient acquired in hospital a catheter-associated infection caused by *P. aeruginosa*. A 10-day course of netilmicin resulted in clinical improvement and eradication of the organism from the urine; however, asymptomatic bacteriologic relapse occurred within 8 days.

Three patients had gram-negative bacillary bacteremia not associated with urinary tract infection. One had *E. coli* bacteremia following excision of an abdominal wall mass, one had mixed *E. coli* and *Klebsiella* sp. bacteremia secondary to acute pancreatitis, and one had *Enterobacter* sp. bacteremia of unknown cause following multiple trauma in a motor vehicle accident. The bacteremias were cured by netilmicin therapy given for 7, 10 and 14 days respectively.

Three patients had soft tissue infections caused by *P. aeruginosa*. Netilmicin therapy resulted in clinical and bacteriologic cure in one and clinical improvement but persistence of the organism in the other two, who had serious underlying diseases; subsequent therapy with another aminoglycoside antibiotic failed to eradicate the infecting organism in either patient.

Seven patients had osteomyelitis. One patient, infected with *Serratia marcescens*, was responding well to netilmicin therapy when he died of an acute cerebrovascular accident during the fourth week of therapy. No organism could be cultured from specimens collected post mortem, and histologic examination revealed healing osteomyelitis. The infecting organism in each of the other six patients was *P. aeruginosa*. Two patients received therapy that was inadequate for evaluation of outcome. Cure was obtained in two patients treated with netilmicin and carbenicillin for 4 weeks, and in one patient treated with netilmicin alone for 4 weeks. The other patient received a 6-week course of netilmicin and carbenicillin for chronic osteomyelitis. Although there was some clinical improvement the infecting organism was not eradicated. Two further long courses of therapy with tobramycin and carbenicillin were also unsuccessful.

One patient had a pericholecystic abscess caused by *E. coli* and *Bacteroides fragilis*. A 2-week course of netilmicin therapy and surgical drainage resulted in initial clinical improvement; however, clinical and bacteriologic relapse occurred within 1 month.

Postoperative septic arthritis due to *Enterobacter* sp. in one patient was cured clinically and bacteriologically by a 3-week course of netilmicin.

The mean serum netilmicin concentrations 1, 2 and 4 hours after the injection of 1.5 mg/kg in patients with normal renal function are shown in Table II. The peak concentrations were slightly higher following intravenous administration than following intramuscular administration.

Toxicity

Injections of netilmicin were well tolerated by all patients, without significant local reaction. Serial audiograms were obtained in 34 patients

Table II—Mean serum netilmicin concentrations after injection of 1.5 mg/kg of body weight in patients with normal renal function

Route of administration	No. of patients	No. of determinations	Mean serum concentrations ± standard deviation (μg/mL) at 1 hour	2 hours	4 hours
Intramuscular	12	23	5.0 ± 1.4	3.7 ± 1.4	2.2 ± 0.9
Intravenous	8	18	5.4 ± 1.7	3.1 ± 0.9	1.7 ± 0.5

having 35 courses of therapy. One patient showed a significant hearing loss in one ear. Otologic investigation revealed this to be a conductive loss without evidence of alteration in neurosensory function, and it was therefore thought not to be related to netilmicin therapy. Hearing remained unchanged in all other patients tested. Dizziness developed in one patient on the sixth day of therapy. True vertigo was not described and there was no nystagmus. Continued dizziness necessitated that the drug's administration be stopped after 7 days of therapy, and the dizziness resolved. The patient's age (88 years) and underlying disease (cerebrovascular accident) could have contributed to the development of dizziness. Although the peak drug concentrations (6.5 and 5.7 μg/mL) were not unusually high in this patient, the trough concentrations (3.0 and 3.7 μg/mL) were elevated. The dizziness might therefore have been related to unusually long periods during which the serum netilmicin concentration was greater than 2 μg/mL. This mechanism may be similar to that suggested by Dahlgren, Anderson and Hewitt[14] in relating gentamicin nephrotoxicity to elevated trough concentrations.

Serum creatinine data adequate for analysis of nephrotoxicity were available for 36 courses of netilmicin given to 35 patients. Significant elevation of the serum creatinine value was detected in five patients; the mean elevation was 0.7 mg/dL and the range was 0.5 to 0.9 mg/dL. In one patient the serum creatinine value rose by 0.5 mg/dL on the fifth day of therapy, but was normal on the seventh day and remained so for a further week of therapy. In the other four patients the elevation was noted near or at the end of therapy. The values returned to baseline in each patient within 6 weeks after the end of therapy.

Liver function was evaluated in 33 patients given 34 courses of netilmicin therapy. Significant elevation of the serum alkaline phosphatase value occurred transiently in two patients. It rose from 127 to 175 IU/L in one patient and from 75 to 145 IU/L in the other. One patient had received the drug intravenously and the other had received it intramuscularly. Results of other liver function tests remained normal in both patients. An additional patient, who was receiving netilmicin intravenously, showed transient elevation of the serum glutamic oxaloacetic transaminase value, from 38 IU/L initially to 75 IU/L by the end of a 4-week course of therapy. Results of other liver function tests in this patient remained normal. In each patient the liver function abnormalities disappeared after cessation of netilmicin therapy.

Discussion

In this study netilmicin was found to be effective in the treatment of serious aerobic gram-negative infections. Clinical improvement occurred in 36 (97%) of 37 evaluable infections. Of 35 infections that were bacteriologically evaluable 30 (86%) were cured. In the one clinical failure and four of the five bacteriologic failures the infecting pathogen was *P. aeruginosa*. The other bacteriologic failure may have been due to inadequate surgical drainage. These proportions are comparable to those of other reported studies. Klastersky and colleagues[4] reported a favourable clinical response in 70% and bacteriologic cure in 53% of 30 patients with serious gram-negative infections and underlying malignant disease. Panwalker and associates[15] have recently reported 100% clinical cure and 96% bacteriologic cure in 27 patients, 24 of whom were infected with Enterobacteriaceae. Their one bacteriologic failure was in a patient with soft tissue infection due to *P. aeruginosa*. In a preliminary report on 26 infections in 25 patients Edelstein and Meyer[16] found an overall favourable response in 81%.

In a controlled study the therapeutic efficacy of gentamicin was found to be 78%, while that of amikacin was found to be 77%.[13] Another controlled study found the efficacy of tobramycin and netilmicin to be similar in the treatment of complicated urinary tract infections.[17] It appears that the efficacy of netilmicin may be similar to that of other aminoglycoside antibiotics.

Similar therapeutic serum concentrations of netilmicin were readily achieved by both the intramuscular and intravenous routes. The mean peak concentration in the patients with normal renal function was 5.0 μg/mL following intramuscular administration and 5.4 μg/mL following intravenous administration.

The potential advantage of netilmicin is its reduced potential for ototoxicity. Studies in animals have indicated almost complete lack of ototoxicity.[9] In this study only one evaluable patient (3%) manifested an adverse reaction (dizziness) that could be attributed to the drug's ototoxicity. In another patient a conductive hearing loss developed that was thought to be unrelated to netilmicin therapy. Other investigators have reported a similarly low frequency of ototoxic effects in humans treated with netilmicin.[4,15,16,18] Further studies, including objective measures of vestibular function, are required to delineate the drug's potential ototoxicity.

Nephrotoxic effects occurred in five patients (or in 5 [14%] of 36 evaluable courses of therapy) and were considered definitely related to netilmicin. The effects were mild and reversible with discontinuation of the drug. In one report granular casts developed in 46% of patients and "significant" elevation of the blood urea nitrogen or serum creatinine concentration, or both, in 30%.[4] However, more than half of the affected patients had received a high daily dose, 7.5 mg/kg, and the criteria for "significant" elevation were not given. Panwalker and colleagues[15] found a 16% frequency of nephrotoxic effects in their series of patients. Thus, the frequency of nephrotoxic effects of netilmicin therapy appears to be similar to that reported for gentamicin, amikacin and tobramycin.[13,19,20]

Panwalker and colleagues[15] also reported that the serum alkaline phosphatase value rose in 43% of patients treated with netilmicin. In our series this value rose in two patients (or in 2 [6%] of 34 evaluable

courses of therapy); in both instances the elevation was mild and reversible. One additional patient had transient mild elevation of the serum glutamic oxaloacetic transaminase value.

Another potential advantage of netilmicin may be its efficacy in the treatment of infections caused by gentamicin-resistant aerobic gram-negative bacilli. Since all the patients in this study were infected with gentamicin-susceptible organisms we were not able to confirm the clinical applicability of this in vitro advantage.

Netilmicin appears to be effective in the treatment of aerobic gram-negative infections. Studies to date in humans indicate that its nephrotoxicity is similar to that of other aminoglycoside antibiotics. Our data do not confirm the high frequency of elevation of the serum alkaline phosphatase value reported by Panwalker and colleagues;[15] however, there does appear to be a low frequency of transient alterations in liver function that has not been reported for other aminoglycosides. The frequency of ototoxic effects of netilmicin therapy appears to be low. Controlled comparative studies are needed to properly evaluate the potential usefulness of this new aminoglycoside antibiotic.

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