ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1978, p. 832-836
0066-4804/78/0013-0832$02.00/0

Vol. 13, No. 5
Printed in U.S.A.

Pharmacology and Efficacy of Netilmicin

IRWIN TRESTMAN, JAMES PARSONS, JEROME SANTORO, GLENN GOODHART, AND DONALD KAYE*

Department of Medicine, The Medical College of Pennsylvania and the Philadelphia V.A. Hospital, Philadelphia, Pennsylvania 19129

Received for publication 21 November 1977

Twenty-six patients, 20 to 77 years of age, were treated with netilmicin, mean dose 2 mg/kg every 8 h intramuscularly or in a 20-min intravenous infusion. The mean serum half-lives in patients with creatinine clearances of ≥90 ml/min and 60 to 90 ml/min were 3.2 and 3.4 h, respectively. In patients with serum creatinines of ≤1.4 mg/100 ml and creatinine clearances of ≥60 ml/min, mean serum levels were 9.0 and 1.2 μg/ml, respectively, 5 to 15 min and 7.5 h post-intravenous infusion, and 7.1 and 1.7 μg/ml, respectively, 1 and 8 h post-intramuscular injection. Twenty-five patients had acute pyelonephritis; 7 of the 25 had bacteremia. The infecting bacteria were *Escherichia coli* (15), *Proteus mirabilis* (5), *Pseudomonas aeruginosa* (2), *Klebsiella pneumoniae* (1), *Enterobacter hafniae* (1), and both *Proteus rettgeri* and *Proteus morganii* (1). All were inhibited by 6.3 μg of netilmicin per ml, except for the *P. rettgeri*, which required 25 μg/ml for inhibition. Of 23 patients who could be evaluated, 19 were bacteriologically and clinically cured at follow-up. Of the remaining four, one relapsed, two became reinfected, and one was lost to follow-up. Five patients developed nephrotoxicity; two of the five had previous renal insufficiency. Three patients, one with abnormal renal function, developed ototoxicity detected only with audiograms. These studies suggest that netilmicin is effective in serious gram-negative bacillary infections, but is nephrotoxic and ototoxic in humans.

The aminoglycosides gentamicin, tobramycin, and amikacin have all proved to be useful agents in therapy of serious infections caused by gram-negative bacilli. These antibiotics are nephrotoxic and ototoxic. Netilmicin, a new aminoglycoside with broad-spectrum activity against gram-negative bacilli, has been shown to be less nephrotoxic and ototoxic than gentamicin in experimental animals (3, 15, 18).

The purpose of this study was to investigate the pharmacology and efficacy of netilmicin in patients with suspected bacteremia caused by gram-negative bacilli.

MATERIALS AND METHODS

Twenty-six patients with suspected bacteremia caused by gram-negative bacilli were hospitalized at either the Hospital of the Medical College of Pennsylvania or the Philadelphia Veterans Administration Hospital. There were 21 females and 5 males, 20 to 77 years of age (mean age, 42). Twenty-four patients were initially treated with netilmicin doses of 1.5 to 2.5 mg/kg of body weight intravenously or intramuscularly every 8 h (with a mean of 2.0 mg/kg). Dosage was modified if renal function was found to be impaired or if netilmicin serum levels were excessive. Two patients initially received 0.7 mg/kg every 8 h because of renal insufficiency. If infection caused by gram-positive cocci was suspected, nafcillin was included initially (three patients).

Netilmicin was given intravenously over a 20-min period; peak serum levels were obtained 5 to 15 min postinfusion and trough levels 7.5 h later. With the intramuscular route, peak serum levels were obtained 1 h postinjection and trough levels at 8 h postinjection. Serum antibiotic levels were usually obtained on days 1, 4, 7, and 10 of therapy. For determination of the half-life ($T_{1/2}$) in serum, multiple blood specimens were obtained after a dose (usually on day 3 to 6). Urine specimens were collected over an 8-h dosing period between days 3 and 7 of therapy. Serum and urine were stored at −20°C until antibiotic levels were measured. An agar diffusion method with paper disks was used for the determination (13). This method has an error of ±10%. Serum $T_{1/2}$ of netilmicin were calculated using the method of least squares (11). Only the beta elimination phase was calculated.

The minimal inhibitory concentration of both netilmicin and gentamicin against the infecting organism was determined by an antibiotic dilution method in heart infusion broth (14). The minimal inhibitory concentration was the lowest concentration of antibiotic that prevented visible growth at 24 h of incubation.

Catheterized or clean midstream urine cultures were obtained prior to, during, and at the end of therapy, and at the follow-up visit. All but one patient were seen in follow-up. Follow-up was at 9 to 32 days after completion of therapy, except for one patient

seen 50 days after therapy. Blood cultures were obtained before treatment and, if positive, were repeated during therapy.

Complete blood count, blood urea nitrogen, serum creatinine, liver function tests (including serum glutamic oxaloacetic transaminase, bilirubin, and alkaline phosphatase), and urinalysis were usually performed on the first day of therapy, during treatment, at the end of therapy, and at the follow-up visit. At least one creatinine clearance was obtained during the course of treatment. Audiograms were obtained as soon as possible after initiation of therapy, during treatment, at the end of therapy, and at the follow-up visit.

RESULTS

Twenty-five patients had acute pyelonephritis with peak temperatures of at least 101°F (ca. 38.3°C) and were treated for 5 to 12 days. Nine of these patients had at least one episode of urinary infection during the preceding year; one of these patients had an ileal loop with renal calculi, two had indwelling Foley catheters, one had a urethral diverticulum, and two had ureteral obstruction. No infecting organism was isolated from the blood or urine of the remaining patient, who was suspected of having pyelonephritis, and therapy was discontinued after 48 h; the patient was later proven to have a tumor. The infecting bacteria were *Escherichia coli* in 15 patients, *Proteus mirabilis* in 5, *Pseudomonas aeruginosa* in 2, *Klebsiella pneumoniae* in 1, *Enterobacter hafniae* in 1, and both *Proteus rettgeri* and *Proteus morganii* in the same patient. Seven had bacteremia (5 *E. coli*, 1 *P. mirabilis*, and 1 *E. hafniae*). All bacteria were inhibited by 6.3 μg of netilmicin per ml, except for the *P. rettgeri*, which required 25 μg/ml for inhibition. The minimal inhibitory concentrations of gentamicin and netilmicin closely paralleled each other.

All 25 patients responded clinically to treatment, and blood and urine cultures were negative after 24 h of therapy. In two patients, treatment was changed to another antibiotic after 5 days because of ototoxicity in one and a preference for another antibiotic by the responsible physician in the other. The remaining 23 patients were treated for 7 to 12 days. Nineteen of them were bacteriologically and clinically cured at the time of follow-up. Of the remaining four patients, one (with renal calculi and an ileal loop) relapsed with *P. aeruginosa* after therapy was stopped, the second had become reinfected with an enterococcus at follow-up, the third had become reinfected with *Serratia marcescens*, and the fourth was lost to follow-up. Thus, the original infection was eradicated in 21 of the 22 patients (95%) in whom treatment could be evaluated.

The mean serum $T_{1/2}$ ± standard deviation (SD) in 14 patients with creatinine clearances of ≥90 ml/min at the time of determining the $T_{1/2}$ was 3.2 ± 1.0 h (range, 1.8 to 5.8). The $T_{1/2}$ ± SD was essentially the same, 3.4 ± 1.1 h (range, 1.7 to 4.6), in 4 patients with creatinine clearance rates of 60 to 90 ml/min. Three patients had a creatinine clearance of <60 ml/min at the time of determination of the $T_{1/2}$. The creatinine clearance and $T_{1/2}$ were as follows: creatinine clearance of 39 ml/min with a $T_{1/2}$ of 6.3 h, creatinine clearance of 31 ml/min with a $T_{1/2}$ of 6.9 h, and creatinine clearance of 32 ml/min with a $T_{1/2}$ of 8.6 h.

Peak and trough serum levels of netilmicin in patients receiving 1.8 to 2.2 mg/kg of body weight every 8 h, who had serum creatinine of ≤1.4 mg/100 ml and creatinine clearance of ≥60 ml/min at the time of the determinations, are shown in Table 1. Peak and trough levels were obtained in 11 patients after intravenous administration of netilmicin. The mean peak ± SD was 9.0 ± 4.3 μg/ml (range, 3.2 to 19.9), and the mean trough was 1.2 ± 0.7 μg/ml (range, 0.3 to 2.8). Antibiotic levels were obtained in 14 patients after intramuscular injections with a mean peak of 7.1 ± 1.4 μg/ml (range, 4.9 to 13.1) and a mean trough of 1.7 ± 1.1 μg/ml (range, 0.5 to 4.3).

The mean urine concentration in patients receiving 1.8 to 2.2 mg of netilmicin per kg of body weight every 8 h with serum creatinine of ≤1.4 mg/100 ml and creatinine clearance of ≥60 ml/min was 177 ± 70 μg/ml (range, 67 to 286) over the 8-h dosage period, and 113 ± 38% of the dose was excreted over 8 h. Patients with creatinine clearances of 31 to 39 ml/min also had high

TABLE 1. *Serum levels (μg/ml) of netilmicin in patients*[a]

Dose route	No. of determinations	No. of patients	Peak mean ± SD (range)[b]	Trough mean ± SD (range)[b]
Intravenous	22	11	9.0 ± 4.3 (3.2–19.9)	1.2 ± 0.7 (0.3–2.8)
Intramuscular	21	14	7.1 ± 1.4 (4.9–13.1	1.7 ± 1.1 (0.5–4.3)

[a] Patients had creatinine levels of ≤1.4 mg/100 ml and creatinine clearance levels of ≥60 ml/min, and received 1.8 to 2.2 mg of netilmicin per kg of body weight every 8 h.

[b] The means of determinations on each patient were used to find the mean of each group.

urine levels; levels were 201, 57, and 219 μg/ml in three patients receiving 0.7, 0.7, and 2.0 mg of netilmicin per kg, respectively.

Five patients developed evidence of nephrotoxicity during or after therapy. Two of the five had renal insufficiency prior to netilmicin. The serum creatinine levels of these patients rose from 1 to 1.4, 1.0 to 1.7, 1.3 to 3.9, 1.5 to 3.2, and 1.8 to 4.7 mg/100 ml, respectively. In four of the five patients, renal function returned toward the base line on subsequent follow-up, and the remaining patient died of a cerebrovascular accident.

Audiograms were obtained in 23 of the 25 patients who were treated for at least 5 days. Three patients, two with normal and one with impaired renal function, developed ototoxicity detected by audiograms. The hearing deficits remained clinically asymptomatic in all three patients. The first was a 27-year-old female with normal renal function, who developed unilateral high-frequency hearing loss (≥4,000 Hertz) from a threshold of 30 decibels to 80 decibels at the end of therapy; no follow-up could be obtained. The second was a 20-year-old female with normal renal function, who developed low (≤500 Hertz)- and high (≥2,000 Hertz)-frequency hearing loss in one ear from a threshold of 20 decibels to 40 decibels; it was totally reversible. The third patient was a 62-year-old female with renal insufficiency, who developed irreversible bilateral high-frequency hearing loss (≥6,000 Hertz) from a threshold of 40 decibels to a threshold of 90 decibels.

Table 2 shows the peak and trough levels of the patients who developed evidence of toxicity. The levels were obtained prior to the development of toxicity. In the five patients who developed nephrotoxicity, the mean peak level after intravenous administration was 6.5 ± 3.2 μg/ml (range, 3.2 to 12.8), and the mean peak after intramuscular administration was 6.8 ± 1.0 μg/ml (range, 6.1 to 8.2). The mean troughs after intravenous and intramuscular administration were 2.3 ± 1.3 μg/ml (range, 0.3 to 4.0) and 3.3 ± 2.0 μg/ml (range, 0.5 to 5.0), respectively. In the three patients who developed ototoxicity, mean peak and trough levels after intramuscular administration were 6.3 ± 0.3 μg/ml (range, 5.2 to 7.6) and 1.5 ± 1.0 μg/ml (range, 0.5 to 2.9), respectively; none received intravenous netilmicin. In the patients with serum creatinine of ≤1.4 mg/100 ml and creatinine clearance of ≥60 ml/min, excluding those patients developing nephrotoxicity or ototoxicity, mean peak levels after intravenous and intramuscular administration were 9.9 ± 4.2 μg/ml (range, 4.0 to 19.9) and 7.3 ± 1.5 μg/ml (range 4.9 to 13.1), respectively. The mean trough levels in this group were 1.1 ± 0.5 μg/ml (range, 0.6 to 2.2) and 1.8 ± 0.8 μg/ml (range, 0.9 to 3.0), respectively. The mean trough levels were higher in those who developed nephrotoxicity than in those who did not. However, the mean peak and trough levels in those developing nephrotoxicity did not differ significantly from the levels in those not developing toxicity ($P > 0.05$); this is true even if the levels with intravenous and intramuscular administration are combined for each group. If only the three patients who developed nephrotoxicity without previous renal insufficiency are considered, the mean trough is only 1.8 ± 1.0 μg/ml. It is interesting that the mean peak level in those developing ototoxicity was significantly lower ($P < 0.05$) than the level in those not developing toxicity, and the mean troughs were similar in the two groups.

No other evidence of toxicity was detected.

DISCUSSION

In both the present study and in studies reported by others (5, 7, 10, 12), netilmicin and gentamicin have been found to have similar activity against most gram-negative bacilli.

TABLE 2. *Serum levels (μg/ml) in patients with and without evidence of toxicity*

Toxicity	Dose route	No. of determinations	Peak mean ± SD (range)[a]	Trough mean ± SD (range)[a]
Nephrotoxicity (5 patients)	Intravenous	8	6.5 ± 3.2 (3.2–12.8)	2.3 ± 1.3 (0.3–4.0)
	Intramuscular	3	6.8 ± 1.0 (6.1- 8.2)	3.3 ± 2.0 (0.5–5.0)
Ototoxicity (3 patients)	Intramuscular	3	6.3 ± 0.3 (5.2- 7.6)	1.5 ± 1.0 (0.5–2.9)
No toxicity (11 patients[b])	Intravenous	16	9.9 ± 4.2 (4.0–19.9)	1.1 ± 0.5 (0.6–2.2)
	Intramuscular	15	7.3 ± 1.5 (4.9–13.1)	1.8 ± 0.8 (0.9–3.0)

[a] The means of determinations on each patient were used to find the mean of each group.
[b] Patients had serum creatinine levels of ≤1.4 mg/100 ml and creatinine clearance rates ≥60 ml/min.

However, netilmicin has also been reported to be active against many gentamicin-resistant strains (7, 10, 12).

The mean peak and trough levels found in the present study are comparable to those reported by Welling et al. (21). Welling et al. gave 2 mg of netilmicin per kg intravenously to patients with normal renal function (creatinine clearance of >100 ml/min) over a period of 2 min, and obtained a mean serum concentration of 11.2 μg/ml 30 min later, 9.3 μg/ml at 45 min, and 1.1 μg/ml at 8 h. In the present study, 1.8 to 2.2 mg/kg was given intravenously over a period of 20 min to patients with relatively normal renal function (serum creatinine of ≤1.4 mg/100 ml and creatinine clearances of ≥60 ml/min). After 5 to 15 min, the mean peak serum concentration was 9.0 μg/ml, and 7.5 h later the mean trough level was 1.2 μg/ml.

The mean serum $T_{1/2}$ (beta elimination phase) for netilmicin was 1.7 h and 3.3 h, respectively, in young healthy volunteers in the studies of Riff and Moreschi (20) and Meyers et al. (16). In the study by Welling et al. (21), the $T_{1/2}$ was 2.1 h for older men with a creatinine clearance of >100 ml/min. The mean serum $T_{1/2}$ was 3.2 h in the present study for patients with creatinine clearances of ≥90 ml/min. A comparable mean serum $T_{1/2}$ (3.4 h) was observed with creatinine clearances of 60 to 90 ml/min. With creatinine clearance rates of 30 to 40 ml/min, the serum $T_{1/2}$ ranged from 6.3 to 8.6 h. There is no apparent explanation for the differences in the $T_{1/2}$ in the studies reported by different authors.

Netilmicin has been found to be less nephrotoxic than gentamicin in animals (3, 15). Fanning et al. (6) reported a 10.5% incidence of nephrotoxicity in patients receiving more than 180 mg of gentamicin daily. Dahlgren et al. (4) found that one-third of patients receiving a loading dose of 2 mg of gentamicin per kg and then 1.5 mg/kg every 8 h developed an elevated serum creatinine. Others (2, 22) have described nephrotoxicity in 30 to 42% of patients receiving even lower doses. In the present study, 5 of 25 patients (20%) treated for at least 5 days developed nephrotoxicity. This is comparable to the 20% incidence of a rise in blood urea nitrogen and/or creatinine observed by Klastersky et al. (12) with the same dose. It should be noted, however, that these doses of netilmicin (i.e., 2 mg/kg every 8 h) were higher than in the gentamicin studies.

Two of the five patients who developed nephrotoxicity had prior renal insufficiency, whereas the remaining three had normal renal function prior to therapy. The peak netilmicin levels were not correlated with the development of nephrotoxicity. However, the trough levels were higher in those who developed nephrotoxicity. Dahlgren et al. (4) found that gentamicin trough levels of >2 μg/ml correlated with development of nephrotoxicity. The elevation of serum creatinine was transient in four of five patients; one patient died of a cerebrovascular accident.

Netilmicin has been shown to be less ototoxic in animals than gentamicin (18). Gentamicin has been reported to cause ototoxicity in from 2 to 18% of patients treated, and vestibular function is affected much more often than auditory function (1, 8, 9, 17, 19). The apparent discrepancy in reported incidences of ototoxicity is probably due to differences in the patient populations studied (i.e., low risk versus high risk) and differences in the extent to which audiometric and vestibular function studies were performed during and after treatment. It is often difficult to determine whether all of the patients in the reported gentamicin studies underwent audiometric testing. Lack of audiograms would give a falsely low frequency of toxicity, because the hearing loss is usually present only at very high frequencies not detectable without audiograms (1, 9).

In the present study, 3 of 23 patients (13%) treated for at least 5 days developed evidence of ototoxicity, and only auditory function was affected. The ototoxicity was reversible in one patient and permanent in the second, and the third patient was lost to follow-up. Only one of the three patients had renal insufficiency. Peak and trough serum levels were not correlated with ototoxicity. In fact, lower peaks were observed in those that developed ototoxicity than in those that did not.

It is clear that, in this study and one other published paper (12), netilmicin was effective in treatment of serious infections. Since a comparable group of patients was not treated with gentamicin in parallel, the relative toxicity of these two aminoglycosides could not be fairly compared. Moreover, the dosage of netilmicin used in this study was higher than that used in other previously reported studies of gentamicin. Further controlled studies using equivalent doses will be necessary to evaluate the toxicity of netilmicin as compared with gentamicin in humans.

ACKNOWLEDGMENTS

This study was supported in part by the Schering Corporation, Bloomfield, N.J.

We thank Alan Rosenberg and Virginia Simpson for technical assistance.

LITERATURE CITED

1. **Arcieri, G. M., F. G. Falco, H. M. Smith, and L. B. Hobson.** 1970. Clinical research experience with gentamicin: incidence of adverse reactions. Med. J. Aust. 1(Suppl.):30–33.

2. **Bodey, G. P., E. Middleman, T. Umsawadi, and V. Rodriguez.** 1972. Infections in cancer patients. Results with gentamicin sulfate therapy. Cancer **29**:1697–1701.
3. **Bowman, R. L., F. J. Silverblatt, and G. J. Kaloyanides.** 1977. Comparison of the nephrotoxicity of netilmicin and gentamicin in rats. Antimicrob. Agents Chemother. **12**:474–478.
4. **Dahlgren, J. G., E. T. Anderson, and W. L. Hewitt.** 1975. Gentamicin blood levels: a guide to nephrotoxicity. Antimicrob. Agents Chemother. **8**:58–62.
5. **Eickhoff, T. C., and J. M. Ehret.** 1977. In vitro activity of netilmicin compared with gentamicin, tobramycin, amikacin, and kanamycin. Antimicrob. Agents Chemother. **11**:791–796.
6. **Fanning, W. L., D. Gump, and H. Jick.** 1976. Gentamicin- and cephalothin-associated rises in blood urea nitrogen. Antimicrob. Agents Chemother. **10**:80–82.
7. **Fu, K. P., and H. C. Neu.** 1976. In vitro study of netilmicin compared with other aminoglycosides. Antimicrob. Agents Chemother. **10**:526–534.
8. **Hewitt, W. L.** 1974. Gentamicin: toxicity in perspective. Postgrad. Med. J. **50**(Suppl. 7):55–59.
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. **Kabins, S. A., C. Nathan, and S. Cohen.** 1976. In vitro comparison of netilmicin, a semisynthetic derivative of sisomicin, and four other aminoglycoside antibiotics. Antimicrob. Agents Chemother. **10**:139–145.
11. **Kaye, D., M. E. Levison, and E. D. Labovitz.** 1974. The unpredictability of serum concentrations of gentamicin: pharmacokinetics of gentamicin in patients with normal and abnormal renal function. J. Infect. Dis. **130**:150–154.
12. **Klastersky, J., F. Meunier-Carpentier, L. Coppens-Kahan, D. Daneau, and J. M. Prevost.** 1977. Clinical and bacteriological evaluation of netilmicin in gram-negative infections. Antimicrob. Agents Chemother. **12**:503–509.
13. **Labovitz, E., M. E. Levison, and D. Kaye.** 1974. Single-dose daily gentamicin therapy in urinary tract infection. Antimicrob. Agents Chemother. **6**:465–470.
14. **Levison, M. E., R. Knight, and D. Kaye.** 1972. In vitro evaluation of tobramycin, a new aminoglycoside antibiotic. Antimicrob. Agents Chemother. **1**:381–384.
15. **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.
16. **Meyers, B. R., S. Z. Hirschman, G. Wormser, and D. Siegel.** 1977. Pharmacokinetic study of netilmicin. Antimicrob. Agents Chemother. **12**:122–123.
17. **Meyers, R. M.** 1970. Ototoxic effects of gentamicin. Arch. Otolaryngology. **92**:160–162.
18. **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.
19. **Nordstrom, L., G. Bangk, S. Belfrage, I. Juhlin, O. Tjernstrom, and N. G. Toremalm.** 1973. Prospective study of the ototoxicity of gentamicin. Acta Pathol. Microbiol. Scand. **241**(Suppl.):58–61.
20. **Riff, L. J., and G. Moreschi.** 1977. Netilmicin and gentamicin: comparative pharmacology in humans. Antimicrob. Agents Chemother. **11**:609–614.
21. **Welling, P. G., A. Baumueller, C. C. Lau, and P. O. Madsen.** 1977. Netilmicin pharmacokinetics after single intravenous doses to elderly male patients. Antimicrob. Agents Chemother. **12**:328–334.
22. **Wilfert, J. N., J. P. Burke, H. A. Bloomer, and C. B. Smith.** 1971. Renal insufficiency associated with gentamicin therapy. J. Infect. Dis. **124**(Suppl.):S148–S153.