Comparison of Netilmicin with Gentamicin in the Therapy of Experimental *Escherichia coli* Meningitis

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Netilmicin (SCH 20569), a new broad-spectrum aminoglycoside derived from sisomicin, was compared with gentamicin in the therapy of experimental *Escherichia coli* meningitis in rabbits. Meningitis was produced in 48 animals by the intracisternal inoculation of 10^5 *E. coli* colony-forming units. The minimum bactericidal concentration was 2 µg/ml against the test strain for both gentamicin and netilmicin. The two aminoglycosides demonstrated comparable penetration into the cerebrospinal fluid (CSF). The mean percent penetration [(CSF concentration/serum concentration) × 100%] was 22.5 ± 6.0 and 20.6 ± 7.2 for netilmicin and gentamicin, respectively ($P = 0.18$). However, netilmicin achieved bactericidal activity in the CSF at lower levels than did gentamicin. When mean CSF concentrations ranged from 4 to 8 µg/ml, mean CSF bacterial titers decreased 2.98 logs in rabbits treated with netilmicin but only 0.16 log in rabbits treated with gentamicin. A 2-log decrease in CSF bacterial counts was produced by a mean CSF concentration of 1.4 µg of netilmicin per ml as compared to 14.1 µg of gentamicin per ml. Because of its reduced toxicity and greater in vivo bactericidal activity, netilmicin may offer an advantage over gentamicin in the therapy of gram-negative bacillary meningitis.

Netilmicin is a new aminoglycoside with a wide in vitro spectrum of activity against most gram-negative aerobic bacilli (2, 3, 7–10, 12, 14, 20–22, 24, 27, 28, 30). The in vivo antibacterial activity of netilmicin is comparable to that of gentamicin (22), and it is active against many gentamicin-resistant strains possessing adenylating enzymes (2'-ANT). Netilmicin was less toxic than gentamicin in chronic dosing studies in cats; i.e., cats receiving 40 mg of gentamicin per kg per day developed ataxia in 10 to 18 days, whereas no ataxia was observed in 3 months with the same dose of netilmicin (22). Similarly, less oto- and nephrotoxicity was observed in rats receiving netilmicin than in those receiving gentamicin (16).

Aminoglycosides remain the most effective antibiotics in the treatment of meningitis caused by *Enterobacteriaceae* and by *Pseudomonas* species. However, the mortality rate and rate of neurological sequelae of such infections in both children and adults remain high (5, 13, 17, 19, 25, 26). Aminoglycosides have been shown to penetrate into the cerebrospinal fluid (CSF) to approximately 20% of simultaneous serum concentrations, thus producing marginal or suboptimal antimicrobial activity in the CSF for most gram-negative bacilli. In a previous study from this laboratory (29), sisomicin was found to possess greater in vivo antibacterial activity in the CSF than gentamicin, tobramycin, or amikacin. Because netilmicin is the 1-ethyl derivative of sisomicin and also exhibits less toxicity, larger doses may be used and bactericidal CSF drug concentrations may be achieved.

The purposes of this study were: (i) to compare the penetration of netilmicin and gentamicin into the CSF; and (ii) to determine the concentration of each drug required to produce bacterial killing in the subarachnoid space in vivo.

MATERIALS AND METHODS

In vitro studies. A clinical bloodstream isolate of *Escherichia coli* which has been previously characterized (29) was used in these experiments. This isolate is K_1^+. The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of each drug were determined in heart infusion broth (Difco) by serial twofold dilutions with both standard test tubes and a microtiter technique (18). The MIC was defined as the lowest concentration of drug inhibiting visible turbidity after 18 h of incubation at 35°C. The MBC was the lowest concentration achieving complete sterility of the wells after 48 h of incubation at 35°C, determined by subculturing onto Trypticase soy agar (Difco) plates. The MICs and MBCs were determined for gentamicin and netilmicin at pH 7.40 and 7.10. Time-kill studies were performed in 25-

ml cotton-stoppered flasks containing heart infusion broth, 10^5 colony-forming units (CFU) of an 18-h culture of *E. coli* per ml, and either gentamicin or netilmicin at concentrations of 0, 2, 4, 8, or 16 μg/ml. Flasks were incubated at 37°C in 5% CO_2 and shaken continuously, and samples were removed at 2, 4, 8, and 24 h and cultured quantitatively. Time-kill studies were done in duplicate with identical results. In addition, time-kill studies were performed in infected CSF in vitro. CSF was removed from nine rabbits with *E. coli* meningitis (see below) 16 h after intracisternal inoculation. The CSF was pooled, and 0.95-ml samples were placed in nine Falcon tubes. Netilmicin or gentamicin (final concentrations, 2, 4, 8, and 16 μg/ml) was added to each tube except the control, which received 0.05 ml of saline. The tubes were placed upright in 25-ml flasks and shaken continuously at 200 rpm in a 5% CO_2 incubator at 37°C. Samples were removed at 0, 2, 4, 6, and 8 h and quantitatively titrated.

Rabbit model. Two-kilogram New Zealand white rabbits were prepared according to the method of Dacey and Sande (6). A dental acrylic helmet was attached to the animal's skull, which allowed the rabbit's head to be immobilized in a stereotaxic frame. A Quincke spinal needle (25 gauge by 3.5 inches [ca. 9 cm]) was introduced into the cisterna magna without trauma by a geared electrode introducer. These needles were used for both inoculation and CSF sampling during the course of treatment.

Experimental design. After withdrawal of 0.5 ml of normal CSF, 10^5 CFU of *E. coli* taken from an 18-h culture, in a volume of 0.2 ml, were inoculated intracisternally. The needle was withdrawn, and the animals were returned to their cages. Eighteen hours later, the rabbits had meningitis characterized by fever >39.6°C, neurological signs, CSF pleocytosis (500 to 25,000 leukocytes/mm³; >95% polymorphonuclear leukocytes), and CSF bacterial titers of 10^2 to 10^7 CFU/ml.

Before initiation of therapy, animals were anesthetized with 30 mg of sodium pentobarbital IV (Barber Veterinary Supply Co., Inc., Richmond, Va.), had indwelling femoral and venous catheters inserted (Intramedic polyethylene tubing 7420, Becton, Dickinson and Co., Parsippany, N.J.), and were repositioned in the stereotaxic frame with the spinal needle reinserted in the cisterna magna. All treatment schedules were for 8 h. Both drugs (supplied by Schering Corp., Kenilworth, N.J.) were dissolved in 34 ml of 0.9% NaCl and administered via constant infusion through the femoral venous catheter by a Sage syringe infusion pump (model 351). Three dosages (50, 100, or 200 mg/8 h) were used, and 20 rabbits were treated with each drug. The animals were kept lightly anesthetized with <10 mg of pentobarbital per kg per h. Eight rabbits received no treatment and served as controls.

Arterial blood samples (3 ml) and simultaneous CSF samples (0.2 ml) were collected at 0, 2, 4, 6, and 8 h of therapy. CSF samples were cultured quantitatively by using serial 10-fold dilutions in 0.9% saline and Trypticase soy agar pour plates. Serum and the remainder of the CSF sample were kept at −70°C until antibiotic assays were made (within 2 weeks). This period of storage did not affect the assay results.

Antibiotic assays. Serum and CSF concentrations of both drugs were determined by using a multidrug-resistant strain of *Staphylococcus epidermidis* (ATCC 27626) by the agar well diffusion technique described by Alcid and Seligman (1). All specimens and standards were tested in triplicate. No zone of inhibition was observed with either serum or CSF from untreated, infected rabbits in this assay system. Standards for serum levels were diluted in normal rabbit serum. CSF standards were diluted in normal saline after zone sizes had been found to be equivalent with dilution in normal saline, normal rabbit CSF, or infected rabbit CSF.

Analysis of data. The percent penetration of drug into the CSF is defined by the formula: percent penetration = (CSF concentration/serum concentration) × 100%. All statistical analysis except for that in Fig. 3 was done on paired data by using Student's *t* test. To analyze the covariance of the data presented in Fig. 3, an F test was utilized (4).

RESULTS

In vitro aminoglycoside activity. The mean MIC at pH 7.40 was 2 μg/ml for both gentamicin and netilmicin. Corresponding MBCs were identical. The mean MBC was increased to 4.4 (range, 1 to 8) and 4.8 (range, 2 to 8) at pH 7.10 for gentamicin and netilmicin, respectively ($n = 7$).

The results of the in vitro time-kill studies in broth are presented in Fig. 1. At 4, 8, and 16 μg/ml, both antibiotics exhibited rapid bactericidal activity with sterile cultures at 2 to 8 h. Both drugs produced sterile cultures in 2 h at 8 and 16 μg/ml and by 8 h at 4 μg/ml. At 2 μg/ml, both antibiotics reduced titers by 2 to 3 logs in 8 h, but values were equivalent to those of controls after 24 h of incubation.

Results of time-kill studies performed in infected CSF in vitro (Fig. 2) were similar to results obtained with time-kill studies in broth when the concentration of antibiotic was 2 μg/ml. However, when higher concentrations (4, 8, or 16 μg/ml) of either antibiotic were used in the infected CSF, bacterial titers decreased to the same extent as when 2 μg/ml was added, which is a reduced bactericidal activity over that observed in broth, where these concentrations resulted in sterile flasks by 2 to 8 h. The initial titer of the infected CSF in vitro was $\log_{10}$ 5.559 ± 0.058 CFU of *E. coli* per ml in the reaction tubes, which is similar to titers obtained in infected CSF in vivo (see below). The control (saline) titer decreased 1.338 logs in 8 h, whereas in all the other samples (both drugs at 2, 4, 8, or 16 μg/ml) the titer decreased 3 logs (netilmicin, 2.662 ± 0.086; gentamicin, 2.967 ± 0.039; $P < 0.001$ versus controls). Therefore, both drugs exhibited essentially identical MICs, MBCs, and rates of bacterial killing in vitro.
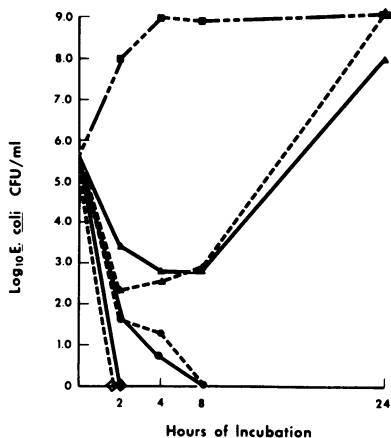
FIG. 1. *Rate of killing of E. coli in broth by gentamicin (- - - -) and netilmicin (——). Concentrations of antibiotics:* ▲, *2 µg/ml;* ●, *4 µg/ml;* ◆, *8 and 16 µg/ml;* ■, *control (— — — —).*
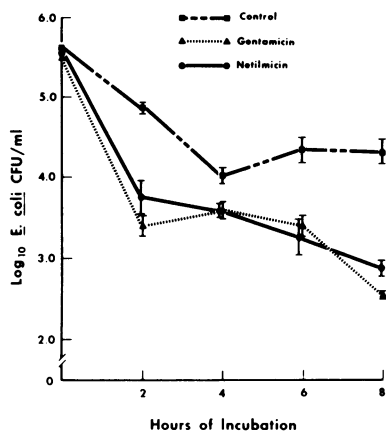

FIG. 2. *Rate of killing of E. coli in infected rabbit CSF in vitro by netilmicin and gentamicin versus controls. Brackets indicate mean ± SD. Each point represents the mean log₁₀ E. coli titer for concentrations of 2, 4, 8, and 16 µg/ml for each antibiotic.*

Penetration into CSF. Serum and CSF concentrations in experimental meningitis varied considerably, but equal dosages of the two aminoglycosides tended to produce serum and CSF concentrations within similar ranges, except at the 50-mg/8 h dose (Table 1). For the 50-mg/8 h dose, serum levels approximated peak therapeutic levels in patients, whereas CSF levels were generally <3 µg/ml. Both concentrations increased over the 8-h treatment period. Serum levels varied more than CSF levels for each antibiotic.

Serum drug levels were comparable at both the 100- and 200-mg dosages. At the 100-mg dosage, mean ± standard deviation (SD) CSF concentrations for netilmicin were 8.9 ± 3.2 µg/ml; in contrast, gentamicin levels were 6.3 ± 4.8 µg/ml. With a dosage of 200 mg over 8 h, the mean ± SD CSF concentrations for netilmicin were 9.7 ± 3.8 µg/ml; however, gentamicin levels were 14.2 ± 4.1 µg/ml. There was considerable overlap in the observed values at all dosages.

The percent penetration, defined as the CSF concentration expressed as a percentage of the concurrent serum concentration, of netilmicin was comparable to that of gentamicin (Table 1). Netilmicin penetrated well even at the lowest dosage used (50 mg/8 h), 22.7 ± 6.3%. The mean percent penetrations at the 200-mg dosage were 19.7 ± 5.1 and 19.6 ± 3.1% for netilmicin and gentamicin, respectively. These values for netilmicin are similar to those observed for four other aminoglycosides in a recent study (29). The percent penetration increased with the hours of therapy at all dosages, indicating that the CSF concentration increased proportionately more than the serum concentration. A significant correlation was not found between the percent penetration of either drug and the initial CSF bacterial titer or leukocyte count. The overall percent penetration was 22.5 ± 6.0 and 20.6 ± 7.2% for netilmicin and gentamicin, respectively (*P* = 0.18). Netilmicin does not

TABLE 1. *Aminoglycoside serum and CSF concentrations and penetration into the CSF in experimental E. coli meningitis*

Antibiotic	Dosage (mg/8 h)	No. of animals	Mean ± SD		
			Serum concn (µg/ml)	CSF concn (µg/ml)	Penetration (%)[a]
Netilmicin	50	6	7.3 ± 5.8	1.4 ± 0.7	22.7 ± 6.3
	100	7	25.7 ± 11.3	8.9 ± 3.2	25.2 ± 6.0
	200	7	51.6 ± 22.9	9.7 ± 3.8	19.7 ± 5.1
Gentamicin	50	7	12.5 ± 5.8	2.9 ± 2.3	23.5 ± 10.8
	100	7	25.4 ± 9.1	6.3 ± 4.8	18.4 ± 4.2
	200	6	52.2 ± 7.2	14.2 ± 4.1	19.6 ± 3.1

[a] Percent penetration = (CSF/serum) × 100%.

differ significantly from gentamicin in its ability to penetrate into the CSF (P range, 0.06 to 0.42).

Bacterial killing. Bacterial killing in vivo was examined in the CSF of 20 rabbits treated with gentamicin and in 20 rabbits treated with netilmicin. Eight untreated, infected rabbits exhibited stable CSF titers of bacteria over the 8-h period of therapy, and all died 24 to 48 h after inoculation. All control untreated animals had initial CSF titers $>10^3$ CFU/ml; therefore, bacterial killing in the treated animals was examined in rabbits with initial titers of the same magnitude. The initial CSF bacterial titer was not different for the two treatment groups (Table 2). Bacterial killing was similar when mean CSF concentrations were in the same range even when initial CSF bacterial titers were variable. For example, with netilmicin, a mean CSF concentration of 7.1 µg/ml produced −3.246 logs in CSF titers when the initial titer was 3.246; when the mean CSF concentration was 7.6 µg/ml, the change in bacterial titer was −3.201 logs in spite of a much higher initial titer of 6.505. This phenomenon was found for all CSF levels for both netilmicin and gentamicin.

Both drugs exhibited bactericidal activity in vivo. Twenty-five of 40 rabbits treated with netilmicin or gentamicin sustained more than 1-log decreases in their CSF bacterial titers during therapy. For netilmicin, the mean decreases in CSF bacterial titers were 1.9, 3.0, and 3.9 logs when the mean CSF concentration ranged from 0.6 to 4, 4 to 8, and >8 µg/ml respectively (Table 2). In contrast, the mean change in CSF bacterial titers for gentamicin were +0.4, −0.2, and −2.0 logs when mean CSF concentrations were grouped in the identical ranges. The differences between the two drugs for all mean CSF concentration groups are statistically significant ($P <$ 0.01). Only when CSF concentrations exceeded 8 µg/ml did gentamicin lower bacterial titers when they were compared with those of untreated rabbits. In contrast, bacterial titers were significantly decreased ($P < 0.001$) by netilmicin for all three CSF ranges. Even when CSF concentrations were <4 µg/ml, the mean change in

CSF bacterial titer was −1.9 logs with netilmicin in spite of a mean CSF concentration of 1.7 ± 1.1 µg/ml, which is similar to the MBC (2 µg/ml) for the test strain determined in broth.

The minimal CSF concentration of each drug producing 2 logs of bacterial killing in 8 h in vivo was determined from the mean CSF concentration (Fig. 3). This concentration was 1.4 µg/ml in 20 rabbits treated with netilmicin and 14.1 µg/ml in 20 rabbits treated with gentamicin. In 10 rabbits treated with gentamicin, no reduction in bacterial titers was observed in spite of mean CSF concentrations of 1.3 to 14.7 (mean ± SD = 4.3 ± 4.1 µg/ml). A 1-log reduction in bacterial titers required a mean CSF gentamicin concentration of 8.8 µg/ml. In contrast, four of six animals with netilmicin CSF concentrations between 0.6 and 2.4 µg/ml exhibited >1-log reductions in bacterial titers, and all 16 animals with mean CSF netilmicin concentrations >1.2 µg/ml demonstrated >1-log reductions. Both lines in Fig. 3 were derived by the method of least squares, and the slopes are significant by the t test (T = 3.476 at 18 df, $P < 0.01$ for netilmicin;
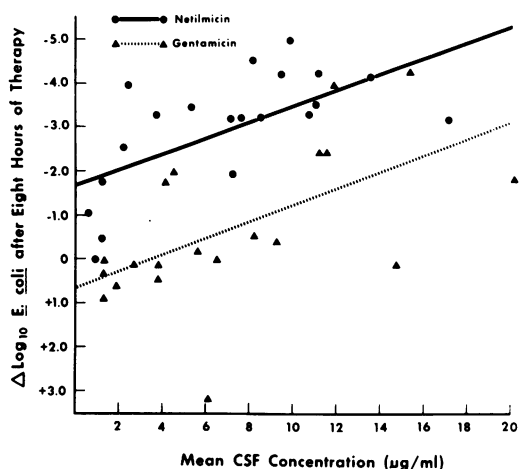

FIG. 3. *Change in CSF titers of E. coli in vivo after 8 h of therapy with gentamicin or netilmicin; all dosage groups. Each point represents one animal.*

TABLE 2. *Bacterial killing by aminoglycosides in experimental E. coli meningitis*

Antibiotic	No. of animals studied	Range of mean drug concn in CSF (µg/ml)	Initial titer (log₁₀ bacteria/ml, mean ± SD)	Change in bacterial titer after 8 h of therapy (log₁₀ bacteria/ml, mean ± SD)
None	8	0	5.115 ± 1.107	+0.099 ± 0.584
Netilmicin	7	0.6–4	4.938 ± 1.467	−1.884 ± 1.480
	4	4.0–8.0	4.756 ± 1.510	−2.970 ± 0.687
	9	>8.0	4.998 ± 1.301	−3.939 ± 0.643
Gentamicin	7	1.3–4.0	4.938 ± 1.371	+0.352 ± 0.314
	5	4.0–8.0	4.336 ± 1.440	−0.162 ± 1.322
	8	>8.0	4.522 ± 0.996	−2.014 ± 1.619

T = 2.912 at 18 df, $P < 0.01$ for gentamicin). The lines also differ significantly from each other by analysis of the covariance of the data (F = 46.16 at $1/37$ df_1/df_2; $P < 0.001$). Thus, although both drugs demonstrated increased bacterial killing in vivo with increased CSF concentrations, netilmicin achieved a bactericidal effect at significantly lower CSF concentrations than did gentamicin.

DISCUSSION

In this study, the comparative values of netilmicin in CSF penetration and in vivo bacterial killing in an experimental model of *E. coli* meningitis were determined. Netilmicin offered no advantage over gentamicin in penetration into the CSF but achieved significantly better in vivo bactericidal activity.

There is a striking animal-to-animal variation in serum levels for both drugs even at identical dosages. This likely reflects the severity of illness of the infected rabbits during the treatment period. When the aminoglycosides are administered to noninfected animals, reproducible steady-state serum levels are achieved. For example, when gentamicin was administered by constant intravenous infusion at 2.5 mg/kg per h to five animals, serum levels of 6.3 ± 1.7 µg/ml (SD) were achieved at 2 h and serum levels of 7.0 ± 0.7 µg/ml were achieved at 8 h. Similar consistent results were seen at other dosages.

CSF gentamicin concentrations achieved in this study are similar to those reported in patients after combined systemic and intrathecal therapy. In adult patients receiving combined intramuscular and intralumbar gentamicin, peak lumbar CSF concentrations have been 19 to 46 µg/ml (25, 26). In another study of gentamicin and tobramycin, peak lumbar CSF concentrations were 27 to 81 µg/ml after intralumbar administration and 12.8 to 40 µg/ml in ventricular fluid after intraventricular administration (11). However, when only systemic gentamicin therapy was used, peak CSF concentrations were <0.9 µg/ml in spite of serum levels in the therapeutic range (13). Chang et al. (5) analyzed simultaneous serum and CSF gentamicin and kanamycin concentrations by radioimmunoassay in 10 neonates with meningitis; although serum levels were therapeutic, only 1 of the 14 CSF samples had a detectable drug concentration. Gram-negative bacillary meningitis is frequently characterized by recurrent relapses and treatment failure, with a high mortality rate (11, 13, 19, 25, 26). Many authors have recommended combined intrathecal and systemic aminoglycoside therapy to ensure high CSF drug concentrations. In this study, netilmicin offered no advantage in percent penetration into the CSF of rabbits, although larger doses and therefore higher serum levels may be feasible, ensuring thereby a higher concentration of drug in the CSF.

There is little correlation between the relative activities of the two drugs determined in vitro and the concentration required to initiate bacterial killing in vivo in this model of gram-negative bacterial meningitis. Several clinical studies (15, 17) have demonstrated that successful therapy of gram-negative bacillary meningitis in infants requires gentamicin concentrations greatly in excess of the MBC. Similar results have been observed in adult cases (25, 26). In a previous study of experimental *E. coli* meningitis, Strausbaugh et al. (29) demonstrated a definite disparity between in vitro and in vivo bactericidal activity. Bacterial killing in vivo required CSF aminoglycoside concentrations that were two to five times the MBC. The best results were obtained with sisomicin. In this study, netilmicin, the 1-ethyl derivative of sisomicin, demonstrated significantly increased bactericidal activity in vivo over that of gentamicin and of three other aminoglycosides evaluated previously (29) in spite of identical MICs, MBCs, and rate of bacterial killing in vitro. Of importance is the fact that netilmicin produced bacterial killing in vivo at or near the MBC determined in vitro, an effect that was not observed with any of the other aminoglycosides. The explanation for this enhanced in vivo activity of netilmicin is currently under investigation. It cannot be explained by the observed acid pH of infected CSF (30), since the MBC rises with a reduction of pH to 7.1 for both drugs. Likewise, it is not due to an inhibitor of gentamicin activity in infected CSF, since both drugs demonstrate equal bactericidal activity in infected CSF in vitro (Fig. 2).

E. coli and *Klebsiella* species remain the most common organisms isolated in cases of gram-negative bacillary meningitis (19, 25). These organisms, including some gentamicin-resistant strains, are susceptible to netilmicin in vitro (2, 3, 7–10, 12, 14, 20–22, 24, 27, 28, 31). Although netilmicin is somewhat less active against *Pseudomonas aeruginosa* (the third most common isolate in cases of gram-negative bacillary meningitis) in vitro than gentamicin, some strains have shown inhibition by a synergistic combination of netilmicin and carbenicillin (2, 10). In a recent review (19), 47 of 61 cases of gram-negative bacillary meningitis were caused by these three organisms. Since netilmicin may offer a lowered toxicity (16, 22) among aminoglycosides, a wide in vitro spectrum against the causative organisms, comparable penetration

into the CSF, and enhanced in vivo bactericidal activity over other aminoglycosides, this agent may prove valuable in the treatment of gram-negative bacillary meningitis. Whether adequate CSF netilmicin concentrations can be achieved in humans with meningitis following only parenteral administration is presently unknown. In these studies, high, potentially toxic, steady-state serum levels of netilmicin were necessary to produce bactericidal activity in the CSF. As with other aminoglycosides, intrathecal administration may well be required to achieve effective CSF activity against most pathogens.

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