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Pharmacokinetic Study of Netilmicin

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Netilmicin at a dose of 2 mg/kg was infused intravenously into 10 healthy volunteers. A peak serum concentration of 16.56 μg/ml was obtained at the end of the infusion. Thirty-nine percent of the infused dose was excreted in the urine during the first 8 h after infusion. The pharmacokinetic parameters of netilmicin were derived by analyzing the elimination data according to a two-compartment model.

The new aminoglycoside netilmicin (Sch 20569), the 1-*N*-ethyl derivative of sisomicin, is active against a wide variety of gram-negative bacteria, including many strains that are resistant to gentamicin, sisomicin, and tobramycin (5, 7, 8). This report presents the results of studies to determine the pharmacokinetic parameters of netilmicin.

Ten healthy volunteers, three male and seven female, with an average weight of 67 ± 10 kg (mean ± standard deviation) and a mean body surface area of 1.84 ± 0.3 m^2, ages 23 to 62 years, were the subjects of this study. Informed consent was obtained from all volunteers, in accord with institutional policies. The volunteers were given a 2-mg/kg dose of netilmicin diluted in 500 ml of 5% dextrose-water and infused intravenously over a 30-min period. Blood samples were obtained just prior to injection and then at 1, 3, 5, 7, 10, 20, and 40 min and at 1, 2, 4, 6, 8, and 24 h after infusion. Urine specimens were collected from 0 to 8 and 8 to 24 h after drug administration. All volunteers were in the fasting state, had voided before injection of the drug, and remained sedentary during the study period. The volunteers had normal hemograms and normal values for serum urea nitrogen, creatinine, bilirubin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, uric acid, albumin, and globulin before and after the study.

Blood specimens were centrifuged after clotting at room temperature for 1 h. Sera and filtered urine specimens were frozen and stored at −70°C. A modified agar plate assay using paper disks (6.35 mm, Schleicher & Schuell Co.), with *Staphylococcus epidermidis* as the test organism, was used to determine netilmicin concentrations (5); all assays were repeated at least three times.

A program written for a Wang 700B programmable calculator was used to analyze the pharmacokinetic data. The data were fitted to two regression lines, and the following pharmacokinetic parameters, based on a two-compartment model (1), were calculated: elimination constant (per hour), *Ke*; transfer constants between the central (V_1) and peripheral (V_2) compartments (per hour), K_{12} and K_{21}; "concentration times time" area below the curve (micrograms per milliliter per hour), *A*; total apparent volume of distribution (by the area method [1]) (liters per 100 kg), *Vd*; plasma clearance (per 1.73 m^2 of body surface area) (milliliters per minute), *C*; half-life of the alpha-elimination phase (hours), $t_{1/2}\alpha$; and half-life of the beta-elimination phase (hours), $t_{1/2}\alpha$. The corrections given by Loo and Riegelman (2) were used for the calculation of the pharmacokinetic parameters.

The mean serum concentrations obtained after 30-min intravenous infusions of 2-mg/kg doses of netilmicin are listed in Table 1. The peak serum concentration was found usually during the first 10 min after completion of the infusion. The mean peak serum concentration observed was 16.56 μg/ml (Table 1). The serum concentrations of netilmicin decreased during the following 8 h, and no drug was detectable at 24 h. Thirty-nine percent of the infused dose of netilmicin was extracted in the urine during the first 8 h after infusion, and only 6.3% was excreted the next 16 h. The average urinary concentration of netilmicin during the first 8 h was 110 μg/ml, and that during the next 16 h was 15 μg/ml.

The pharmacokinetic parameters derived in this study from the mean serum concentrations listed in Table 1 are as follows: *Ke*, 0.42/h; K_{21} and K_{12}, 0.43 and 0.2/h, respectively; *A*, 32.93 μg/ml; $t_{1/2}\alpha$ and $t_{1/2}\beta$, 0.85 and 3.26 h, respectively; *Vd*, 28 liters; and *C*, 64 ml/min.

The elimination data we obtained after in-

TABLE 1. *Serum concentrations of netilmicin after 2-mg/kg intravenous doses infused over 30 min*

Time after end of infusion (h)	Serum concn (μg/ml)
0.0167	16.49 ± 9.1[a]
0.05	16.56 ± 6.8
0.0833	15.85 ± 5.4
0.117	15.31 ± 6.1
0.167	14.90 ± 5.3
0.333	12.87 ± 4.1
0.667	9.75 ± 4.3
1	7.89 ± 2.6
2	3.25 ± 1.4
4	2.14 ± 1.3
6	1.39 ± 0.87
8	0.91 ± 0.41

[a] Mean ± standard deviation.

travenous infusion of netilmicin were best resolved into two regression lines and analyzed by a two-compartment model (1). The prolonged alpha distribution phase of nitilmicin in this study was similar to that we observed with sisomicin (6) and longer than what we previously found for both tobramycin and gentamicin (4). Indeed, the elimination constant, the transfer constants, the apparent volume of distribution, the plasma clearance, and the half-life of the beta-elimination phase determined for netilmicin are very similar to the values we previously found for sisomicin (6).

Serum concentrations of netilmicin after 2-mg/kg intravenous doses, even at 4 h after drug infusion, exceeded the minimal inhibitory concentrations of netilmicin for susceptible gram-negative bacilli (5, 8). The serum concentrations of netilmicin measured at 8 h after infusion were still greater than the minimal inhibitory concentrations of netilmicin for more than 60% of the susceptible gram-negative bacteria, including strains of *Pseudomonas aeruginosa* (5). The urinary concentrations of netilmicin found during the 24 h after intravenous infusion far exceeded the minimal inhibitory concentrations of netilmicin for susceptible gram-negative isolates (5, 8).

The increasing number of clinical isolates found to be resistant to gentamicin mandates the availability of greater numbers of antimicrobial agents effective against such gentamicin-resistant bacteria. Furthermore, recent studies have shown that netilmicin is less nephrotoxic than gentamicin in animals (3, 7). Thus, netilmicin warrants clinical study to determine its effectiveness in the treatment of patients with infections caused by gram-negative bacteria.

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