Concentrations of Vancomycin in Bone and Serum of Normal Rabbits and Those with Osteomyelitis

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The concentrations of vancomycin in the bone and serum of rabbits with Staphylococcus aureus osteomyelitis were assessed after each rabbit was given a single dose of vancomycin. Simultaneous mean concentrations of vancomycin in infected rabbits 1 h after administration of the antibiotic were 36.4 ± 4.6 μg/ml (serum), 5.3 ± 0.8 μg/g (infected bone), and 3.0 ± 0.2 μg/g (noninfected bone). Concentrations of vancomycin in serum of normal controls were higher than concentrations of vancomycin in serum of osteomyelitic rabbits after 1, 2, 3, and 6 h.

There is little published information on the concentration of vancomycin in either normal or infected bone (10). It is important to have such information because that this antimicrobial agent exhibits in the treatment of methicillin-resistant Staphylococcus aureus, methicillin-resistant S. aureus, and enterococcal osteomyelitis. The current study assesses concentrations of vancomycin in the bone and serum of rabbits with S. aureus osteomyelitis. Concentrations of the antibiotic in serum of normal controls and in serum of rabbits with osteomyelitis are also compared.

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The rabbit model (9) utilized in this study was developed by Scheman et al. (13). The strain of S. aureus used in this study was isolated from a patient with osteomyelitis. The strain possesses the following characteristics: it is not susceptible to S. aureus bacteriophages constituting the standard typing set, it is methicillin susceptible and coagulase positive, and it produces β-lactamase and a golden-yellow pigment. Production of osteomyelitis was accomplished by the procedure described previously (8). Progressive destruction of bone with sequestrum formation was present by day 14 (2, 9). At 3 to 4 weeks after induction of osteomyelitis, radiographs were taken to confirm and assess the severity of infection. Subsequently, a single intravenous (i.v.) dose of 30 mg of vancomycin per kg of body weight was given to each of 12 infected rabbits and to each of 6 normal rabbits. Subcutaneous and intramuscular routes of administration did not yield reproducible concentrations of vancomycin in serum. This dosage resulted in optimal concentrations of vancomycin in serum that were below the toxic range 1 h after administration of vancomycin. Concentrations of vancomycin 1 h after administration coincide with the beginning of the elimination phase of vancomycin (7, 12). Vancomycin was dissolved in sterile water, diluted in sterile saline to a concentration of 5 mg/ml, and administered i.v. over a period of 5 min (3). Concentrations of vancomycin in serum and bone (8) were assessed using a modification of the agar disk diffusion bioassay described by Walker and Kopp (14).

The minimum concentrations of vancomycin detectable in this system were 0.78 μg/ml of serum and 0.78 μg/g of bone. Concentrations of vancomycin in serum and in bone were analyzed using the Student's t test. Various parameters of the nonlinear time-concentration relationship (Fig. 1) were estimated from a least-squares linear regression of log-transformed concentration data over time (1, 6). R², the coefficient of determination, represents the proportion of variability in e(y − 3)² accounted for by fitting the straight line. Differences in the slopes of the profiles of vancomycin concentration in serum of noninfected and infected rabbits over time were analyzed by constructing 99% confidence intervals about the slopes of the regression lines, using the t distribution (1).

Concentrations of vancomycin in serum and bone were determined after a single i.v. injection of the antibiotic (30 mg/kg). Assessments of concentrations in infected rabbits were performed 3 to 4 weeks after induction of osteomyelitis. Concentrations of vancomycin in serum were assayed over time in five infected and six noninfected rabbits (Fig. 1). The equation for the least-squares regression line of the noninfected profile was y = 46.67(0.839)x; R² = 0.92. The profile data for the infected rabbits can be described by the equation y = 23.28(0.861)x; R² = 0.84. Concentrations of vancomycin in serum of noninfected rabbits were significantly higher than concentrations in serum of infected rabbits 1, 2, 3, and 6 h after administration of the antibiotic (P < 0.01). However, the slopes of the profiles for noninfected and infected rabbits were not significantly different (99% confidence intervals). At 1 h after administration of vancomycin to seven rabbits with osteomyelitis, concentrations of vancomycin were determined for serum, infected bone (left tibia), and uninfected bone (right tibia) for each of these rabbits. The mean concentration of antibiotic in serum (36.4 ± 4.6 μg/ml) was much higher than that attained in bone. Moreover, mean concentrations in infected bone (5.3 ± 0.8 μg/g) were higher than those in noninfected bone (3.0 ± 0.2 μg/g); this difference was statistically significant (P < 0.02).

The dosage of vancomycin used in this study was based on the necessity to achieve optimal, but nontoxic, concentrations of vancomycin in serum. Neurotoxicity, a problem with vancomycin, appears infrequently when concentrations in serum are below 30 μg/ml but increases in frequency as concentrations reach 80 μg/ml or above (3, 4). Concentrations of vancomycin in serum of noninfected animals 1, 2, 3, and 6 h after administration of a single i.v. dose of vancomycin were significantly higher than those of infected animals. However, the slopes of the lines describing the time-concen-
after induction mean. In this study, the entire tibia was crushed and the mean concentrations of vancomycin were determined for infected and noninfected bones. However, the concentration of vancomycin may vary in different segments of the same bone. The method used for determining the concentration of vancomycin in bone was based upon the underlying assumption that all antibiotic present in the bone could be eluted into the buffer and serum. Thus, the values reported may be a conservative estimate of the actual concentration of vancomycin in bone. The concentration of vancomycin in infected bone 1 h after dosage surpasses the minimum inhibitory concentrations of virtually all pathogenic strains of staphylococci (11). However, it is tenuous to make a conclusion solely on this basis concerning the therapeutic efficacy of vancomycin in the treatment of osteomyelitis. The most important reason is that the minimum inhibitory concentration, an in vitro test, reflects purely the antimicrobial properties of vancomycin; thus, this test may not adequately reflect the complex environment in which the antibiotic must act (5). Also, differences in units of measurement prevent the minimum inhibitory concentration (micrograms per milliliter) from being directly compared with the concentration of vancomycin in bone (micrograms of vancomycin per gram of bone). Further clinical and animal studies are necessary to define the efficacy of vancomycin in the treatment of osteomyelitis caused by organisms susceptible to this antibiotic.

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FIG. 1. Vancomycin serum profiles of six noninfected (—) and five infected (--) rabbits with S. aureus osteomyelitis after a single i.v. injection of vancomycin (30 mg/kg). Concentrations of vancomycin in serum of infected rabbits were determined 3 to 4 weeks after induction of osteomyelitis. Bars represent ± standard error of the mean.