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Gentamicin Intravenous Infusion Rate: Effect on Interstitial Fluid Concentration

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To assess the possible role of intravenous (i.v.) infusion rate as a determinant of degree and rate of interstitial fluid penetration, six rabbits, each with four intraperitoneal implanted capsules, were studied by crossover design after a single dose of 1.7 mg of gentamicin per kg by either slow 2.5-min i.v. bolus or 30 min i.v. infusion. The mean serum peak antibiotic level after slow bolus was 17.4 μg/ml. After 30 min of infusion, mean serum peak was 8.3 μg/ml ($P < 0.025$). Mean capsule fluid antibiotic levels at 30 min, 1, and 2 h were 0.9 μg/ml, 1.6 μg/ml, and 1.8 μg/ml, respectively, after slow bolus and 0.6 μg/ml, 0.9 μg/ml, and 1.3 μg/ml after 30-min infusion ($P < 0.05$ at 30 min, $P < 0.001$ at 1 h, and $P < 0.05$ at 2 h). Comparison of capsule levels beyond 2 h revealed no significant differences, and peak capsular concentrations achieved by the two methods were similar. Slow 2.5-min i.v. bolus administration of gentamicin established higher interstitial fluid levels during the first 2 h of therapy and may be the preferred mode of delivery when rapid extravascular penetration is desired.

A variety of techniques for intravenous (i.v.) gentamicin administration have been described in the literature. They include rapid bolus, with delivery in less than 1 min, slow bolus with delivery in 2.5 to 5 min, and slow continuous infusion over 1 to 2 h. With higher serum levels achieved by bolus administration, speculation has been directed toward possible increased toxicity by this technique; however, many authors have concluded that the more rapid methods of delivery are without increased risk of nephro-, oto-, or neuromuscular toxicity (5, 6, 10). With this in mind, we sought to determine in an animal model the effect of i.v. gentamicin injection rate on the magnitude and rapidity of penetration into interstitial fluid.

MATERIALS AND METHODS

Animal model. By the technique described by Gerding et al., four multiperforated table-tennis balls were implanted by means of midline abdominal incision in the peritoneal cavities of each of six white New Zealand rabbits, under general anesthesia with ketamine hydrochloride (2). On separate days, at least 4 weeks after implantation, the rabbits received, into a marginal ear vein, 1.7 mg of gentamicin per kg either by slow bolus in 2 ml of saline over 2.5 min or by slow infusion in 15 ml of saline over 30 min, accomplished by a Harvard pump (Harvard Apparatus Co., Dover, Mass.). Half the rabbits initially received gentamicin by slow bolus, and half received the drug by slow infusion. Previous studies with this model have demonstrated a capsule-to-capsule variability in antibiotic penetration that has been attributed to differences in the degree of vascularity of the capsules. Because of this variability, a crossover design with paired statistical analysis comparing each capsule to itself by the two methods of delivery was selected. Between 8 and 28 days elapsed before the crossover design was completed. Blood samples were obtained from mammary veins or veins in the opposite ear at times 0, 5, and 30 min, hourly for 6 h, and again at 24 h. By means of direct percutaneous aspiration with a 22-gauge needle attached to a 5-ml syringe, simultaneous fluid specimens from each capsule were obtained at all times except 5 min. Serum was separated and frozen with capsular fluid specimens until antibiotic assays could be performed.

Microbiological assay. Gentamicin assays were performed by overnight disk diffusion on antibiotic medium 5 (Difco Laboratories, Detroit, Mich.), adjusted to pH 8, and seeded with *Bacillus subtilis* ATCC 6633 spores (8). Fluid specimens were placed on 6.35-mm disks (Schleicher and Schuell, Inc., Keene, NH.) using disposable 20-μl capillary pipettes (Unopette, Becton-Dickinson and Co., Rutherford, N.J.). Each specimen was assayed on three plates with four disks per plate, two containing the unknown and two containing a serum reference standard. Plates were incubated 24 h at 37°C. Antibiotic levels were read from a linear standard curve, determined by known concentrations in rabbit serum ranging between 0.125 and 20 μg/ml. These results were shown to be superimposable on a standard curve derived from capsular fluid.

Protein binding. Gentamicin binding to rabbit

serum and capsular fluid was determined by velocity sedimentation in a Beckman L2-65B preparative ultracentrifuge (Beckman Instruments, Inc., Palo Alto, Calif.) (7, 9). Eight-milliliter samples of serum or capsular fluid containing 10 μg of gentamicin and 0.01 μCi of [^{14}C]gentamicin (specific activity, 0.789 μCi/mg) (Schering Corp., Bloomfield, N.J.) per ml of sample were centrifuged at 295,000 × *g* for 3 h at 30 to 35°C. The top 0.5 ml of ultracentrifugate (UC) was removed and assayed for gentamicin activity by both bioassay and radioactivity. Gentamicin activity was also determined in each starting sample (SS), and antibiotic protein binding (%*B*) was determined from the following: %*B* = (1 − UC/SS) × 100%.

Statistics. Statistical analysis was performed by the paired Student's *t* test. Statistical significance was assigned when *P* values were <0.05.

Antibiotic kinetics. Half-lives of gentamicin in serum after slow bolus and slow infusion were calculated from the standard formula, using the slope of the regression line (semilogarithmic plot) determined by the method of least squares from the arithmetic mean of six experiments (3). Area under the curve for both serum and capsular fluid was measured in triplicate by use of a compensating polar planimeter.

RESULTS

Figure 1 illustrates serum and capsular fluid gentamicin levels after both modes of i.v. delivery. Each point on the serum lines represents the mean determination from all six animals. Each point on the capsular fluid lines represents the mean level of 24 capsules.

Five minutes after initiation of slow 2.5-min bolus and 30-min infusion, mean serum levels were 17.4 and 3.2 μg/ml, respectively ($P < 0.025$). At 30 min, serum levels were nearly identical at 8.5 μg/ml and 8.3 μg/ml, respectively. Mean capsular fluid level 30 min after slow bolus was 0.9 μg compared with a level of 0.6 μg of drug per ml after slow infusion. This difference was significant ($P < 0.05$). At 1 h, capsule fluid level was 1.6 μg/ml after bolus and 0.9 μg/ml after slow infusion, a significant difference ($P < 0.001$). At 2 h, mean capsule fluid level was 1.8 μg/ml after bolus administration and 1.3 μg/ml after 30-min infusion, a difference remaining significant ($P < 0.05$). Beyond the 2-h time, there were no significant differences in the capsule fluid levels. At 6 h, levels were nearly identical at 1.1 and 1.2 μg/ml after bolus and slow infusion, respectively.

Mean peak capsular concentration after slow bolus infusion (1.8 μg/ml) occurred at 2 h after administration and was not significantly different from mean peak capsule concentration after 30-min infusion (1.5 μg/ml), which did not occur until 3 h.

The half-lives of gentamicin after 2.5-min bolus and 30-min infusion were calculated to be 1.6 and 1.2 h, respectively. Area under the curve for serum gentamicin level by slow infusion between times 0 and 6 h was 87% that by bolus administration. Area under the curve for capsular gentamicin levels by slow infusion was 83% that by bolus.

Gentamicin binding to rabbit serum and capsular fluid is given in Table 1. Binding to both serum and capsule fluid was low, ranging from 13 to 22% by both bioassay and radioactive gentamicin assay.

DISCUSSION

Factors governing antibiotic penetration into interstitial fluid may be multiple. Protein binding has been deemed particularly important by some. With respect to gentamicin, protein binding in human serum is negligible (4). Binding in rabbit serum performed in our laboratory by an ultracentrifugation technique was compara-

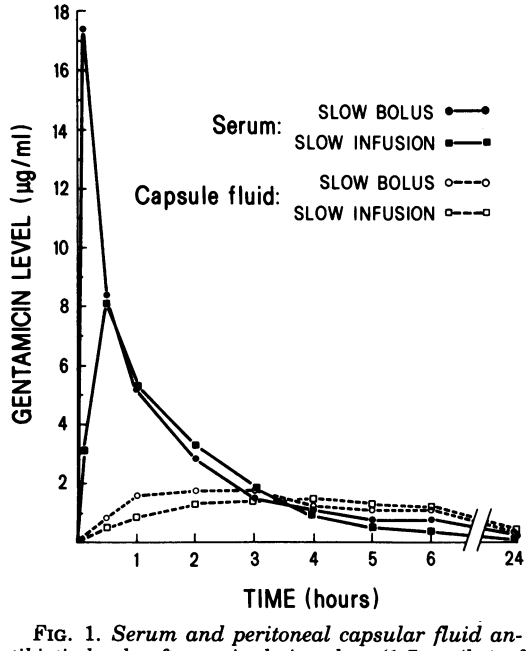

FIG. 1. *Serum and peritoneal capsular fluid antibiotic levels after a single i.v. dose (1.7 mg/kg) of gentamicin by 2.5-min slow bolus and 30-min slow infusion.*

TABLE 1. *Gentamicin binding to rabbit serum and capsular fluid at 10 μg of the drug per ml*

Assay method	Serum (%)	Capsular fluid (%)
Bioassay	21.7 ($n = 2$)[a]	16.7 ($n = 1$)
Radioassay	18.8 ($n = 2$)	13.1 ($n = 1$)

[a] *n*, Number of determinations.

bly low at 21.7%, essentially identical to binding to human serum by the same method (23.2%, unpublished data). Therefore, in rabbit serum, protein binding is similar to binding in human serum and should not constitute a major limiting factor in third-space penetration for gentamicin.

Clearly, differences in rates of antibiotic i.v. delivery establish differences in concentration gradients between serum and interstitial fluid by virtue of higher peak serum levels resulting from more rapid modes of delivery. With drug metabolism and clearance ongoing, an antibiotic more rapidly delivered could be more rapidly cleared, thereby offsetting the advantage of an increased concentration gradient. This did not appear to be the case in our study, since serum antibiotic levels at 30 min were nearly identical by both modes of delivery, and serum levels beyond this point were similar. By bolus administration, there were significantly higher levels of antibiotic in capsular fluid over the first 2 h, with comparative levels beyond this point not significantly different.

We initially anticipated a difference in achievable peak capsular antibiotic concentrations by the two modes of delivery. By our data, we have not observed a significant difference in peak levels of drug achieved (1.8 μg/ml by slow bolus at 2 h versus 1.5 μg/ml by 30-min infusion at 3 h), but we have observed a significant difference in rate at which capsular fluid levels have risen. These small, but statistically significant, differences in capsular fluid levels in the first 2 h after administration suggest that i.v. slow bolus delivery is superior to slow infusion if rapid achievement of interstitial levels is desired. Although the clinical importance of these observations in humans is not known, slow bolus administration appears to be the preferred method in seriously ill patients or in those in need of antibiotic prophylaxis just before or during surgery (1).

Although the meaning and interpretation of capsular fluid levels has been questioned, if cochlear levels of gentamicin are similar to capsular fluid, then from our observations we would speculate that slow bolus administration does not result in higher total drug levels than slow infusion, as is currently postulated, but only results in a more rapid penetration. Clearly, further clinical studies such as that of Mendelson et al. (5) are needed to confirm the safety of slow bolus administration.

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