Comparative Penetration of Amikacin, Gentamicin, and Penicillin G into Exudate Fluid in Experimental Sterile Peritonitis

ROB ROY MacGREGOR

Infectious Diseases Section, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19174

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Using a rabbit sterile peritonitis model, we compared the penetration of intravenously administered amikacin, gentamicin, and penicillin G into peritoneal exudate. Peritonitis was induced with sterile normal saline, and the peritoneal exudate contained $23,751 \pm 3,039$ granulocytes 8 h later. Antibiotics were administered intravenously 3 h after initiating peritonitis, and serum and peritoneal fluid concentrations were measured for 5 h. Peritoneal levels of each antibiotic exceeded simultaneous serum levels by 1 h after dose and remained above serum levels thereafter. The maximum peritoneal fluid concentration of amikacin reached $71.2\% \pm 12.7$ of the maximum serum concentration, whereas maximum gentamicin peritoneal concentration achieved $37.1\% \pm 2.7$, and penicillin achieved $23.2\% \pm 4.5$, of their respective maximum serum concentrations.

Our laboratory has developed a rabbit model for sterile peritonitis (8), which offers the opportunity to study the penetration of various antibiotics into peritoneal exudate. Peritonitis can develop after abdominal surgery, spontaneous rupture of a viscus, in alcoholics with cirrhosis, and as a complication of peritoneal dialysis. In all of these clinical settings, gram-negative rod infections are common, and aminoglycoside antibiotics offer the widest spectrum of effectiveness for these organisms. Because Smithivas et al. (12) had reported that "peritoneal gentamicin levels remained in a suboptimal range despite the development of high levels in the serum" in some patients with peritonitis, we measured the kinetics of gentamicin penetration into peritoneal exudate in our experimental model and compared them with the new aminoglycoside, amikacin. This new drug, produced by acetylation of the deoxystreptamine residue of kanamycin A, is more active than kanamycin against most strains of *Pseudomonas* species, including most of those that have inactivating enzymes for gentamicin, tobramycin, and kanamycin (3). Therefore, it might represent a reasonable antibiotic choice in cases of peritonitis if its penetration into the exudate is adequate. To broaden our comparison of relative efficiency of penetration, we also studied penicillin G, because its structure and pharmacology are quite different from the aminoglycosides, and because much already is known regarding its behavior in the peritoneum (4, 10).

MATERIALS AND METHODS

Sterile peritonitis was induced in 2- to 3-kg New Zealand white rabbits by the instillation of 120 ml of sterile normal saline into the peritoneal cavity through a 16-gauge multiply fenestrated intravenous polyethylene catheter (Deseret Pharmaceutical Co., Sandy, Utah) inserted carefully into the peritoneal cavity to avoid the bowel. During the next 8 h, the catheter was held in place with an elastic bandage, and the peritoneal fluid was sampled at 2-h intervals. The animals developed an acute peritonitis, with mean exudate granulocyte counts of 885 ± 309 (standard error) at 2 h, $10,808 \pm 2,623$ at 4 h, $19,408 \pm 3,733$ at 6 h, and $23,751 \pm 3,039$ at 8 h. The catheter was removed after 8 h and, by 24 h after the saline instillation, the animals had neither physical evidence of continued peritoneal reaction nor any apparent aftereffects.

Peritonitis was allowed to develop for 3 h before antibiotic administration, by which time the animals' abdominal musculature was tense and tender to pressure. At that time, blood and peritoneal exudate fluid was taken for "preantibiotic" measurement, and a dose of the antibiotic to be studied was infused through an ear vein over 2 to 3 min. Blood and exudate samples were drawn at 15 min, and then at 1, 3, and 5 h after the end of infusion. Samples were centrifuged for 15 min at 3,000 rpm, and the clear serum or peritoneal fluid was frozen at -70°C until time of antibiotic assay.

The antibiotic dosages for the rabbits were chosen on the basis of normal doses used in humans: amikacin, 7.5 mg/kg; gentamicin, 2 mg/kg; or penicillin G, 200,000 U/kg. The goal was not to compare the peak concentrations achievable with each of the three antibiotics in peritoneal exudate, but rather to determine how close the peak peritoneal fluid concen-

tration of each drug would come to its peak serum concentration, and to study the pharmacokinetics of the drugs between blood and exudate.

The antibiotics were measured with an agar diffusion assay using *Bacillus globigii* as the test organism (13). Wells were filled with the serum or peritoneal samples from the test animals or with freshly prepared antibiotic standards added to normal rabbit serum, which had been shown previously to give no zone of inhibition on the assay plates. The plates were incubated for 6 h at 37°C, and the zones of inhibition of growth of the test organisms were measured to the nearest 0.1 mm. Standard curves were then constructed for each antibiotic using the number of millimeters of clearing around each well of the standards, and the concentrations in the serum and peritoneal fluid samples were read from the standard curve. Each unknown was run in duplicate, and the results were averaged.

RESULTS

The pharmacokinetics of amikacin and gentamicin in rabbits with sterile peritonitis is shown in Fig. 1. Six animals were given each antibiotic, and each isobar represents plus or minus the standard error of the mean. For both antibiotics, the levels in the peritoneal fluid exceeded those in the serum by 1 h, and thereafter remained above simultaneous serum levels. Figure 2 shows that high doses of penicillin are rapidly excreted: by h 3 after injection, most penicillin had been cleared from the serum, whereas the peritoneal fluid concentrations remained high. Figure 3 displays the peritoneal fluid concentration of each antibiotic as a percentage of the peak serum level for that antibiotic. Amikacin proved most effective in entering the peritoneal exudate, with levels reaching $71.2\% \pm 12.7$ (standard error) of peak serum levels; gentamicin reached $37.1\% \pm 2.7$, and penicillin reached $23.2\% \pm 4.5$.

DISCUSSION

The penetration of aminoglycoside and penicillin antibiotics into the peritoneal space has been studied in settings of ascitic fluid accumulation, peritoneal dialysis, and peritonitis. Ascitic fluid was produced by Gerding et al. by constricting the thoracic inferior vena cava in dogs (Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 15th, Washington, D.C., Abstr. 405, 1975). These investigators reported that both gentamicin and amikacin developed ascites concentrations 17% of those in serum and that the peritoneal levels of the cephalosporins reached 21 to 26% of serum levels. In a different model, Gerding and Hall obtained peritoneal fluid by placing hollow, fenestrated balls in the peritoneal cavity of rabbits and aspirating from them percutaneously thereaf-

FIG. 1. Serum and peritoneal fluid concentrations of amikacin and gentamicin after intravenous administration. Each antibiotic was given 3 h after initiation of sterile peritonitis. The points represent mean concentrations in six animals, and the brackets indicate plus or minus standard errors of the means.

ter (6). The fluid had the characteristics of ascitic fluid: 1,560 leukocytes/mm³, 55% neutrophils, and a protein level of 4.1 g/100 ml. Gentamicin and tobramycin peritoneal levels reached only 16.5% of peak serum levels, but amikacin was more effective, reaching 32.4% of peak serum level. Cephalosporins varied from 11.9 to 26.6% of serum levels.

In studies of antibiotic distribution during peritoneal dialysis, Smithivas reported effluent levels 17.4 and 36.4% of simultaneous serum levels in two patients receiving gentamicin intramuscularly during dialysis (12). Gary stud-

FIG. 2. Serum and peritoneal fluid concentrations of penicillin G after intravenous administration. Conditions parallel Fig. 1.

FIG. 3. Concentration of the antibiotics in peritoneal exudate fluid, expressed as the percentage of peak serum concentration for each antibiotic.

ied two patients during three episodes of dialysis and found serum gentamicin clearance rates of 2.0 to 19.4 ml/min, removing from 286 to 659 μg of the drug per h (5). In a larger group of patients receiving peritoneal dialysis, Mahon et al. found a mean gentamicin clearance rate of 7.5 ± 1.3 ml/min and a gentamicin plasma half-life of 36 h (compared with 8 h in patients on hemodialysis [9]). Data on peritoneal transfer of kanamycin (included because of the similarity of this drug to amikacin [3]) show that one-third of an injected dose is removed in 24 h of peritoneal dialysis, for a clearance rate of 5.3 to 8.3 ml/min (1, 7). Kanamycin plasma half-

life of 70 to 84 h was reduced to 12 h, and recommendations for drug replacement on the day of dialysis suggest either 3.5 mg/kg (1) or a standard dose of 250 mg (7). Madhavan et al. reported that peritoneal dialysis had minimal effect on the serum half-life of amikacin in three patients, and they found levels of 0.7 to 4.98 $\mu\text{g}/\text{ml}$ in the dialysis fluid (T. Madhavan, E. Fisher, K. Burch, E. Haas, F. Cox, K. Yaremchuk, N. Levin, and E. L. Quinn, *Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother.*, 15th, Washington, D.C., Abstr. 89, 1975). For penicillins, Ruedy reported dialysis fluid levels of oxacillin and ampicillin that were 31.2 and 21.3%, respectively, of their serum levels (10), and Sher et al. reported that methicillin levels in the dialysis effluent were 56 and 32% of maximum serum levels in two patients (11). An authoritative guide to therapy in renal failure states that there is "no significant dialysis of penicillin G with peritoneal dialysis" (2).

In cases of active peritonitis, Smithivas reported that passage of gentamicin from serum to dialysate was quite variable, with a mean peritoneal level 23.8% of serum levels during the first 12 h of treatment (12). Therefore, they recommended addition of gentamicin to the dialysis fluid to assure therapeutic levels in the peritoneal space. Gerding et al. reported much more favorable results in patients with alcoholic cirrhosis and spontaneous peritonitis: gentamicin levels in the peritoneal fluid varied from 54 to 117% of serum levels in six patients, tobramycin exudate concentrations were 14 to 100% of serum concentrations in seven patients, and penicillin and ampicillin proportions were 60 to 100% (D. N. Gerding, W. H. Hall, and E. Schierl, *Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother.*, 15th, Washington, D.C., Abstr. 406, 1975).

Our data suggest that both gentamicin and amikacin enter the peritoneal exudate effectively. Therefore, physicians can anticipate therapeutic peritoneal levels when treating peritonitis with either aminoglycoside in doses sufficient to produce high but subtoxic serum levels (e.g., 6 to 10 $\mu\text{g}/\text{ml}$ for gentamicin and 20 to 25 $\mu\text{g}/\text{ml}$ for amikacin). In clinical situations in which the difference between the antibiotic level required for therapeutic effect and the toxic concentration of that drug is small, amikacin may be preferred because a higher percentage of its serum concentration penetrates into the peritoneum.

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