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The Use of Gentamicin in Peritoneal Dialysis. II. Microbiologic and Clinical Results

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Gentamicin was administered in 33 episodes of peritoneal dialysis complicated by persistence of a turbid dialysate. Antibiotic treatment was considered indicated if the effluent from dialysis contained a predominance of polymorphonuclear leukocytes. Bacteria were isolated from the dialysate in approximately 50% of patients, the majority of whom had either fever or abdominal symptoms. In most instances, evidence of infection cleared during therapy with gentamicin or other antibiotics subsequently selected according to microbiologic data. Four patients with bacteriologically confirmed peritonitis, three due to *Pseudomonas aeruginosa* and one to *Staphylococcus aureus*, responded poorly to gentamicin. Prolonged antibiotic therapy resulted in one case of superinfection with *Candida*. Gentamicin is a useful single drug for the initial treatment of potential bacterial peritonitis due to either gram-positive or gram-negative pathogens. However, treatment with a semisynthetic penicillin or cephalothin for staphylococcal peritonitis, and the addition of carbenicillin for peritoneal infection due to *Pseudomonas* appear preferable to the continued use of gentamicin alone. Early consideration of therapy with two agents is warranted in severely ill patients with peritonitis.

Peritoneal dialysis, in this hospital, is a useful alternative to hemodialysis for chronic as well as acute renal failure. Six patients are maintained on a chronic program by three dialyses a week. During a six-month period, 2.8% of dialyses on these patients resulted in a persistently turbid dialysate due to neutrophilic leukocytes. Although causes other than infection have been suggested [1, 2], we chose to institute antibiotic therapy in all such cases when gram stain of the dialysate sediment confirmed a predominance of neutrophils. Because of the efficacy of gentamicin against multiply resistant gram-negative pathogens at our hospital and its in-vitro activity against *Staphylococcus aureus*, we administered this agent during peritoneal dialysis, either by the intramuscular or intraperitoneal route, or by a combination of both. Assays of gentamicin in the serum and dialysate effluent during 24 periods of treatment have formed the basis of a pharmacologic study reported separately [3]. The purpose of this paper is to summarize the clinical features and therapeutic results of our experience.

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Methods

Thirty-three instances of persistently turbid effluent during peritoneal dialysis occurred among 16 patients between April, 1970 and March, 1971. These included individuals undergoing dialysis for both acute and chronic renal failure. Turbidity of the dialysate was evaluated by gross examination of 2 liters in a glass jar. Criteria for antibiotic treatment and inclusion in this study were continued turbidity beyond five or six exchanges and a predominance of neutrophils on gram stain of the sediment. In each case, information was recorded regarding the duration of dialysis, character of the dialysate, bacterial isolates and their antibiotic susceptibility, signs and

symptoms of infection, peripheral leukocyte count, treatment, and result. Permanent (Tenckhoff) peritoneal catheters were present in seven patients. In eight, separate catheters were inserted for each procedure. Dialysis was carried out as previously described [3]. Cultures of peritoneal fluid were obtained by inoculating 10 ml of cloudy dialysate into 50 ml of sterile thioglycollate broth and incubating at 37 C. Treatment with gentamicin was then initiated according to the regimens described in the preceding paper [3].

Results

Bacterial peritonitis. Among 33 episodes of presumed peritonitis treated with gentamicin, 12 were associated with either microbiologic or clinical evidence of acute infection. These findings occurred in 11 patients and are summarized in table 1. A pathogenic organism was recovered from the dialysate during 10 episodes; in one case, sufficient fever, leukocytosis, and abdominal pain were present to warrant a diagnosis of bacterial peritonitis. A high correlation existed between bacteriologic and clinical evidence of peritonitis. Of the 10 cases from which *S. aureus, Pseudomonas* or *Escherichia coli* were isolated, fever of greater than 100 F occurred in eight patients, and abdominal pain or tenderness in eight. However, a peripheral leukocyte count greater than 10,000/mm^3 was present in only three. At least one of these manifestations was present in all individuals considered to have clinical peritonitis. The patient from whom a pathogen was not isolated (one culture yielded diphtheroids) experienced fever greater than 101 F, marked leukocytosis, and definite abdominal symptoms.

Gentamicin alone produced a satisfactory response in two of five patients with peritonitis due to *S. aureus*. A third (with combined staphylococcal and Group A streptococcal infection) had no improvement in abdominal pain 24 hr after the onset of therapy with gentamicin, and a culture of the dialysate taken at that time yielded *S. aureus*. Cephalothin, 100 mg/liter, was added to the dialysis fluid, and cultures became negative. However, abdominal cramps and tenderness continued for three days and finally subsided following the intraperitoneal use of vancomycin, 12.5 mg/liter. Two other patients with staphylococcal peritonitis received oxacillin one day after initial therapy with gentamicin. In both, abdominal pain and dialysate turbidity were unchanged following 24 hr of gentamicin administration; cultures taken just before the addition of oxacillin again yielded *S. aureus*. Gentamicin eradicated *E. coli* from the peritoneal dialysate of one patient. Peritonitis due to *Pseudomonas* was cured by gentamicin alone in only one of four cases. In that instance, both the im and ip routes were used simultaneously and resulted in mild vestibular toxicity. Subsequently, three individuals with this type of infection were treated according to a modification of the regimen derived from the preceding study [3. Table 4 (patients no. 1, 3, and 4) contains the corresponding pharmacologic results]. Gentamicin, 10 mg/liter, was continuously added to the dialysis fluid, and one or two im doses of 80 mg were also given. Levels in both serum and peritoneal dialysate varied between 1.4 and 13.0 μg/ml; however, the minimal bactericidal concentration of gentamicin for these strains of *Pseudomonas* was 3.12–6.24 μg/ml, and the clinical response was poor. All three patients continued to have abdominal pain, and the cultures of dialysate of two repeatedly yielded *Pseudomonas*. Carbenicillin, 2.5 g by iv infusion every 12 hr, was then added to the regimen of each. They also received 100 mg of this drug/liter of dialysis fluid, one for two days and the others for five days. All improved clinically, and the dialysates remained sterile.

Nonspecific peritoneal inflammation. A diagnosis of bacterial peritonitis could not be substantiated by microbiologic or clinical findings on 21 occasions following the administration of gentamicin. In 17 of 21, the dialysate cleared during therapy with gentamicin, and in four, the patients remained asymptomatic following discontinuation of dialysis and antibiotic. One patient, from whom a coagulase-negative *Staphylococcus* was isolated, had a fever of 102 F for one day. This organism was also present in the dialysate of a second patient who remained asymptomatic. Diphtheroids were isolated from the peritoneal fluid of another individual whose highest temperature was 100 F and whose peripheral white-blood-cell count was 15,300/mm^3; there were no abdominal signs and symptoms. Other patients had neither fever, leukocytosis, nor abdominal pain. In addition to the bacteria mentioned above, an alpha hemo-

Table 1. Microbiologic and clinical characteristics of patients with bacterial peritonitis during dialysis.

Patient	Organism*	Temperature†	WBC‡	Abdominal signs and symptoms	Antibiotic treatment	Outcome
1	*Staphylococcus aureus* and unidentified gram-negative bacillus	101.8	9.1	None	Gentamicin ip, 5 mg/liter	Cultures negative and fluid clear after four days.
2	*S. aureus*	100.2	6.0	Pain, tenderness	Gentamicin ip, 5 mg/liter; then oxacillin, 1 g every 4 hr im, and ip, 100 mg/liter	Culture: *S. aureus* 24 hr after gentamicin, then negative with clear fluid after oxacillin.
3	*S. aureus* and *Streptococcus pyogenes*	99.8	16.4	Pain, tenderness	Gentamicin ip, 5 mg/liter; then cephalothin ip, 100 mg/liter and vancomycin ip, 12.5 mg/liter.	Culture: *S. aureus* 24 hr after gentamicin, then negative after cephalothin and vancomycin. Fluid cleared after seven days.
4	*S. aureus* and *Staphylococcus* coagulase-negative	102.4	11.8	Mild tenderness	Gentamicin im, 80 mg twice and ip, 5 mg/liter.	Fluid persistently cloudy for three days, patient removed catheter and remained well.
5	*S. aureus*	101.6	7.6	Pain, tenderness	Gentamicin im, 80 mg twice and ip, 5 mg/liter; then oxacillin 1 g im every 4 hr and ip, 100 mg/liter.	Culture: *S. aureus* 24 hr after gentamicin; then negative with clear fluid after oxacillin.
6	*Pseudomonas aeruginosa*	104	20.9	Pain, tenderness	Gentamicin im, 80 mg every 12 hr and ip, 5 mg/liter. Also, amphotericin B ip, 2.5 mg/liter.	Fluid cloudy and pain persisted after initial gentamicin treatment, followed by several other antibiotics. *Pseudomonas* and *Candida* then repeatedly isolated and eradicated by regimen noted.

(*continued*)

Table 1. (Continued).

Patient	Organism*	Temperature†	WBC‡	Abdominal signs and symptoms	Antibiotic treatment	Outcome
7	*P. aeruginosa*	101	6.6	Pain, tenderness	Gentamicin im, 80 mg and ip, 10 mg/liter; then carbenicillin iv, 25 g every 12 hr and ip, 100 mg/liter.	Cultures: *Pseudomonas* for six days on gentamicin; then negative after carbenicillin; fluid cleared.
8	*P. aeruginosa*	98.6	6.9	Pain, tenderness	Gentamicin im, 80 mg twice and ip, 10 mg/liter; then carbenicillin iv, 2.5 g every 12 hr and ip, 100 mg/liter.	Pretreatment cultures became negative. Cloudy fluid and pain persisted after gentamicin; carbenicillin added with good clinical response.
9	*P. aeruginosa*	101.8	8.5	Pain, tenderness	Gentamicin ip, 5–10 mg/liter for eight days; then im, 80 mg once and carbenicillin iv, 2.5 g every 12 hr and ip, 100 mg/liter.	Cultures: *Pseudomonas* during ip gentamicin for eight days. Cleared two to three days after carbenicillin added.
10	*Escherichia coli*	100.4	5.9	Mild pain	Gentamicin ip, 5 mg/liter.	Cultures became negative after one day; fluid cleared after seven days. *Saccharomyces* isolated on seventh day.
11	Diphtheroid	101.8	21.7	Pain and tenderness	Gentamicin im, 80 mg every 12 hr; then cephalothin iv, 2 g every 12 hr and ip, 100 mg/liter.	Fluid partially cleared after eight days. Dialysis stopped. Patient died eight days later due to myocardial failure. Autopsy: few focal peritoneal adhesions; no active infection.

* Isolated from peritoneal dialysate.
† Highest rectal temperature (°F).
‡ Highest peripheral white blood count per mm^3.

lytic streptococcus was recovered from the dialysate of one patient, and cultures of peritoneal fluid from two asymptomatic individuals yielded both coagulase-negative *Staphlococcus* and enterococci.

Discussion

Peritonitis complicating dialysis is usually defined as a syndrome of abdomnial pain or tenderness, fever, and microbiologic confirmation of peritoneal infection [4, 5]. Isolation of bacteria from the dialysate without concomitant clinical signs of infection is most often considered due to contamination [1, 4, 5]. Turbidity of the dialysate as an isolated event is also not generally considered sufficient evidence for the diagnosis of infection [1, 2]. In our series, a high correlation existed between those with fever, abdominal pain and tenderness, and the subsequent isolation of a pathogen. These patients formed a readily defined group with clinical peritonitis. Those with negative cultures rarely developed signs of infection. However, when persistent turbidity of the dialysate is first evident, a distinction between the two groups cannot be made. Gram stain of the sediment revealed a predominance of neutrophils in all instances but rarely demonstrated bacteria. It is possible that the large volume of dialysate sufficiently diluted the bacterial cultures so that falsely negative cultures may have been obtained before treatment. In such instances, early use of gentamicin could have prevented the development of clinical signs and symptoms. These cases would thus not be included among those with clinically evident peritonitis.

It should be noted that *Pseudomonas* and *Achromobacter,* both resistant to gentamicin, were isolated from one asymptomatic patient during gentamicin therapy but did not produce infection. *Saccharomyces* was recovered from another individual and also was not invasive. The dialysate from a third patient, treated with gentamicin for pseudomonas peritonitis, persistently yielded *Candida* species that required amphotericin B for eradication. Therefore, in order to minimize the threat of superinfection, we have concluded that antibiotic treatment should be stopped when a turbid dialysate persists beyond three days without accompanying bacteriologic or clinical evidence of peritonitis. On each of four such occasions in our experience, patients have remained asymptomatic following withdrawal of therapy. In one, enterococcus was recovered from a catheter tip following its removal. We have been unable to document the degree to which peritoneal catheters contributed to persisting infection or effluent turbidity. In many cases, chronic dialysis was dependent upon the continued use of these catheters; they were thus removed only after antibiotic therapy failed to result in a clear dialysate.

Gentamicin alone was not effective in curing peritonitis due to *S. aureus* and *Streptococcus pyogenes* in one patient, and *Pseudomonas* in three others. Since oxacillin was given 24 hr following gentamicin in two cases (at which time peritoneal cultures were still positive), conclusions regarding the efficacy of the latter drug in staphylococcal peritonitis cannot be drawn. Failure of gentamicin in those patients with peritonitis due to *Pseudomonas* may have been due to the relatively high concentrations required for bactericidal activity against the infecting strains. Pharmacologic results of our study, reported separately, have indicated that in the presence of peritoneal inflammation, a single im dose of gentamicin (80 mg) and simultaneous dialysis with 5 mg of gentamicin/liter of fluid, results in equilibration of antibiotic between the serum and peritoneum at 1.5–5.0 μg/ml. We have subsequently increased this dosage so that two injections of 80 mg, separated by 12 hr, are given while 10 mg/liter is included in the dialysis fluid. However, the concentrations achieved in serum and peritoneal fluid have remained erratic (1.4–13.0 μg/ml) and frequently below those expected. Once equilibration has been achieved, the instillation of 10 mg of gentamicin/liter of dialysis fluid should yield a concentration of 10 μg/ml in the dialysate. It is possible that some inactivation by heparin (10 mg/liter of dialysis fluid) occurs [6]. Gentamicin concentrations of 6.2 μg/ml or greater are required for bactericidal activity against many strains of *Pseudomonas*. Thus, more than 10 mg of gentamicin/liter of dialysis fluid, or the addition of carbenicillin, as in our cases, may be necessary for successful treatment of peritonitis due to this organism.

Oxacillin, 1 g parenterally every 4 hr, is metabolized by uremic patients whether peritoneal dialysis is in progress or not [7]. We have also added 100 mg of this drug to each liter of dialysis fluid

in the treatment of peritonitis due to *S. aureus*. Although a favorable effect of gentamicin on staphylococcal infections has been reported [8], our experience suggests that a semisynthetic penicillin, or cephalothin, is necessary for optimal treatment of peritonitis caused by this organism. Thus, gentamicin alone, in the doses used, has not been consistently effective in eradicating staphylococcal or pseudomonas infection during peritoneal dialysis. While larger doses may yield sufficient concentrations in serum and peritoneum to favorably influence these results, the risk of auditory, vestibular, and renal toxicity would also be increased. Gentamicin is a valuable single drug for the initial treatment of potential gram-positive and gram-negative peritoneal infections. Either oxacillin or carbenicillin may be added according to subsequent bacteriologic and clinical indications. This approach has yielded good results among our patients, although several days were required to control some infections. Since infection due to *S. aureus* and *Pseudomonas* were prominent in this and other series [4, 5], severely ill patients may warrant the early use of combined therapy.

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