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Research Article

Intraperitoneal and Subsequent Intravenous Vancomycin: An Effective Treatment Option for Gram-Positive Peritonitis in Peritoneal Dialysis

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SUMMARY

Intraperitoneal vancomycin absorption is higher when there is peritoneal inflammation, but the absorption decreases with recovery from peritonitis. Consequently, intraperitoneal maintenance doses are ineffective, reducing the rate of cure.

Aim: To evaluate the outcome of Gram-positive peritonitis treated with intraperitoneal and subsequent intravenous vancomycin.

Methods: In April 1996, we initiated a protocol for treating peritonitis caused by Gram-positive organisms using a 2-g intraperitoneal loading dose of vancomycin followed by intravenous vancomycin at 1 g twice in 5 days for coagulase-negative *Staphylococcus* and at 1 g three times in 5 days for *Staphylococcus aureus*. We analyzed episodes of Gram-positive peritonitis (coagulase-negative and *S. aureus*) and the efficiency of the treatment protocol in 113 patients undergoing peritoneal dialysis between 1 April, 1996 and 3 August, 2016. There were 6090 patient-months and the mean treatment lasted 54±44 months. The outcomes were evaluated as (1) complete cure, (2) relapsing peritonitis, (3) catheter removal for refractory peritonitis, and (4) death.

Results: A total of 51 cases of coagulase-negative *Staphylococcus* peritonitis and 37 of *S. aureus* were seen in 46 of the 113 patients (40.7%). Of these, coagulase-negative *Staphylococcus* (92.15%) and 34 *S. aureus* peritonitis (91.89%) resolved.

Conclusion: The response to treatment was very satisfactory.

INTRODUCTION

Since the introduction of continuous ambulatory peritoneal dialysis (CAPD), there have been steady advances in the clinical and laboratory knowledge of infectious complications, the pharmacokinetics of antibiotics and improvements in catheters and devices to avoid peritoneal cavity contamination [1-4]. Nevertheless, peritonitis is the most important clinical complication of CAPD, resulting in 15% technique failure [5] and 2%-3% mortality [6].

Gram-positive peritonitis continues to be common. Several treatments are used, but none is infallible. First-generation cephalosporins and vancomycin used in continuous and intermittent protocols have varying success rates. Bailie and Manley observed vancomycin has an extremely advantageous pharmacokinetic profile, as one single intraperitoneal dose of 15-30 mg/kg results in adequate serum and dialysate concentrations for several days, at least in CAPD patients [7,8].

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Intraperitoneal maintenance doses of vancomycin become ineffective because the intraperitoneal absorption is higher when peritoneal inflammation is present [9-11], but decreases as the patient improves and peritoneal inflammation decreases, falling below the minimum inhibitory concentration and leading to relapse and refractory peritonitis [12].

Therefore, this prospective study evaluated the outcome of Gram-positive peritonitis (coagulase-negative and Staphylococcus aureus) treated with a protocol using intraperitoneal and then intravenous vancomycin.

MATERIAL AND METHODS

In April 1996, we initiated a prospective treatment protocol for coagulase-negative Staphylococcus and S. aureus peritonitis comprising vancomycin at 2 g as an intraperitoneal loading dose, followed by intravenous vancomycin at 1 g twice in 5 days as maintenance treatment for coagulase-negative Staphylococcus and three times in 5 days for S. aureus. In addition, oral rifampin at 600 mg per day was prescribed for 5-7 days for S. aureus peritonitis.

During the period from 1 April, 1996, to 3 August, 2016, 113 patients undergoing peritoneal dialysis were enrolled [42 males (37.16%), mean age 54.19±15 years, total treatment time 6090 patient-months, and mean treatment duration 54±44 months]. Twenty two diabetic patients comprised 19.46% of the all PD patients. We examined the outcomes of all coagulase-negative Staphylococcus and S. aureus peritonitis episodes treated using this protocol from our database.

Peritonitis was defined as the presence of a cloudy dialysis effluent with more than 100 white blood cells/mm^3 and a white blood cell differential count with greater than 50% polymorphonuclear cells, as previously described [13]. As part of the initial empirical therapy, the patients also received an aminoglycoside or third-generation cephalosporin, but these were stopped when the Gram stain or culture results were obtained.

Transfer-sets were changed 7-10 days from the onset of peritonitis when the effluent was clear and patients were symptom-free. Heparin (500-1000 U/L) was given regularly until the effluent was clear. The first cloudy effluent sample was cultured using standard microbiological techniques. We could not analyze all Gram-positive organisms in terms of methicillin resistance. The serum vancomycin levels were not measured.

We analyzed the Gram-positive peritonitis episodes and the treatment efficiency in terms of a 1) complete cure, 2) relapsing peritonitis, 3) catheter removal for refractory peritonitis, and 4) death. We defined complete cure as clinical and laboratory resolution of the episode. Relapsing peritonitis was defined as when an episode occurred within 4 weeks of the completion of therapy for a prior episode caused by the same organism or a negative effluent culture. Refractory peritonitis was defined as the absence of therapy success after 5 days of treatment necessitating catheter removal.

RESULTS

During the study period, 71 of 113 patients (62.8%) developed 185 episodes of peritonitis: 135 during CAPD and 50 during APD (1 episode per 32.92 patient-months, cumulative peritonitis rate 0.365). During this time, 46 of the 113 patients (41.4%) developed 51 episodes of coagulase-negative Staphylococcus peritonitis and 37 episodes of S. aureus peritonitis were recorded. With our treatment protocol, 47 (92.15%) of the coagulase-negative peritonitis episodes resolved and four catheters were removed for refractory peritonitis. In addition, 34 (92%) episodes of S. aureus peritonitis resolved, one patient died, and two catheters were removed. No relapsing

peritonitis was observed. A summary of the outcomes with our protocol of treatment are shown in Table 1. It is also important to highlight that 34 of 37 peritonitis episodes with culture-negative were resolved. No red-neck syndrome was observed with intravenous vancomycin.

DISCUSSION

Peritonitis is the Achilles' heel of peritoneal dialysis, and treatment failure may occur because of methicillin resistance or antibiotic levels below the minimum inhibitory concentration (MIC), probably related to the route of administration, dose, and interval between doses.

Vas et al. [14] used intermittent cefazolin as treatment and reported failure percentages of 0% for coagulase-negative Staphylococcus (methicillin sensitive; MS), 55% for coagulase-negative Staphylococcus (methicillin resistant; MR), and 33% for S. aureus. In patients given 2.0 g of vancomycin intraperitoneally in one bag repeated weekly for two further doses for coagulase-negative Staphylococcus, culture-negative peritonitis, or other Gram-positive organisms and three doses for S. aureus, the failure percentages were 8% for coagulase-negative Staphylococcus (MS), 27% for coagulase-negative Staphylococcus (MR), and 42% for S. aureus. Therefore, the overall methicillin resistance was 39%. Methicillin resistance plays a very important role in treatment failure, and is observed in 15%-20% of S. aureus and 30%-40% of S. epidermidis. The methicillin-resistance rate was 60% for coagulase-negative Staphylococcus and 10% for S. aureus at New Haven University [15], 40% for Gram-positive organisms at Michigan University [16], 60% for S. aureus in Japan [17], and 33% for S. aureus and 80% for S. epidermidis in Brazil [18]. The latter group reported a low cure rate using 1 g of cefazolin once a day and 0.2 mg/kg/day amikacin [18]. Lai et al. reported a 100% response rate for coagulase-negative Staphylococcus and 80% for S. aureus using cefazolin intraperitoneally at 500 mg/L once a day [19]. In addition, in a controlled study, the rate of cure was 84% with intraperitoneal vancomycin compared with 71% using cefazolin via the same route, and catheter loss was observed 1.3 times more often than with cefazolin [20]. Brown et al. observed an 82.5% cure rate with cefazolin once a day [21].

Krothapalli et al. and Obermiller et al. found that intravenous vancomycin was 85% effective for treating Gram-positive peritonitis [22,23]. Using 1 g of intravenous vancomycin weekly for 4 weeks, Mulhern et al. observed initial responses in 31 episodes, but 29% relapsed when the serum vancomycin level was below 12 mg/L (10). In a review of the treatment of Gram-positive peritonitis with intraperitoneal vancomycin, 80-90% of the episodes were eradicated [7]. Vargemezis et al. compared intraperitoneal and intravenous vancomycin, and observed relapsing peritonitis in patients given only two 1-g intravenous doses, the first on admission and the second 7 days later [24]. Similarly, Ballinger et al. found better results with intraperitoneal vancomycin [25].

Considering the increase in vancomycin-resistant organisms, the use of vancomycin as initial therapy is controversial [7]. However, intraperitoneal vancomycin is considered the first option, with first-generation cephalosporins for Gram-positive coverage (26-28). Bastani observed that the absorption of intraperitoneal vancomycin was 74% when there was peritoneal inflammation and 51% with normal peritoneum.

Table 1: Outcomes of coagulase-negative S. and *S. aureus* peritonitis episodes.

Organism	n	Complete cure	Relapsing peritonitis	Catheter removal	Death
Coagulase-negative *Staphylococcus*	51	47 (92.15%)	--	4	--
S. aureus	37	34 (91.89%)	--	2	1

Bunke et al. and Pancorbo et al. found similar levels of absorption (54% and 65%, respectively) with normal peritoneum [9-11].

Considering this, we developed a treatment protocol using intraperitoneal vancomycin initially and intravenous vancomycin for 5 days. Our study was limited because we did not measure the MIC or evaluate methicillin resistance in any patient.

In conclusion, we observed satisfactory treatment outcomes in our series, perhaps because the serum antibiotic levels during the treatment were sufficiently high. Further studies should verify the efficacy of our treatment protocol.

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