Efficacy and Safety of Meropenem Plus Tobramycin Followed by Meropenem Plus Vancomycin for Treating Peritonitis in Patients on Continuous Ambulatory Peritoneal Dialysis

Peritonitis is a serious complication in patients on peritoneal dialysis. We examined the efficacy of MTV therapy [first 7 days: meropenem 0.5 g intravenously (IV) twice daily, plus tobramycin 15 mg intraperitoneally (IP) in every dialysis bag; next 7 days: meropenem 0.5 g IV twice daily, plus vancomycin 8 mg/kg IP in every bag after a 1-g loading dose] on peritonitis in patients undergoing continuous ambulatory peritoneal dialysis (CAPD), comparing it with the treatment previously recommended by the International Society for Peritoneal Dialysis (combination of first-generation cephalosporins and aminoglycosides).

We treated 36 CAPD peritonitis episodes with MTV therapy. Outcome measures were primary response rate at day 14 and relapse rate within 28 days after the start of antibiotic therapy.

The primary response rate was 34/36 (94.4%). No patients treated with MTV therapy required catheter removal. We observed no serious side effects in these patients.

We conclude that MTV therapy may be an even better choice of treatment for peritonitis in patients on CAPD than was the previous empirical treatment (combination of first-generation cephalosporin and aminoglycosides).

Key words
Peritonitis, meropenem, vancomycin, coagulase-negative staphylococci

Introduction
Peritonitis is one of the major complications of continuous ambulatory peritoneal dialysis (CAPD), and it remains the primary reason that patients are switched to hemodialysis (1). The International Society for Peritoneal Dialysis (ISPD) recommends several empirical treatment schedules combining a first-generation cephalosporin and a second-generation cephalosporin or an aminoglycoside until no bacteria can be isolated from the peritoneal dialysis fluid (2).

Recently, two major concerns arose in treatment of peritonitis: one is a change in the profile of the organisms of resistant peritonitis, and the other is the emergence of antimicrobial-resistant gram-positive bacteria. To combat these challenging difficulties in treating peritonitis in patients undergoing CAPD, we focused on the role of meropenem, a carbapenem and a substitute for cephalosporin. Also, because of the high frequency of \textit{Staphylococcus aureus} and coagulase-negative staphylococci (3,4) in PD peritonitis, we continued to use vancomycin despite the ISPD recommendation (5).

In the present study, we examined the efficacy and safety of vancomycin in combination with meropenem as treatment for peritonitis in CAPD patients.

Patients and methods
All stable CAPD patients in the dialysis center who were aged 18 years or older and who developed clinical evidence of peritonitis were eligible for the study. Peritonitis was diagnosed when abdominal pain and
cloudy peritoneal dialysis fluid occurred with or without fever, and when the peritoneal white blood cell (WBC) count was higher than 100 cells/mm³, with more than 50% neutrophils. Informed consent was obtained from each patient. Patients who had known hypersensitivity to cephalosporins, aminoglycosides, or vancomycin; in whom fungal or tuberculous peritonitis was suspected; who had relapsing peritonitis (that is, an episode of peritonitis within 4 weeks after apparent recovery, and cessation of antibiotics from a previous episode of peritonitis); or who had an active exit-site infection were excluded from the study.

Cure was defined as complete resolution of signs and symptoms of peritonitis, with negative peritoneal dialysis fluid cultures and no further episodes of peritonitis within 28 days following cessation of antibiotic treatment. “Primary cure” refers to cure by the assigned intraperitoneal (IP) or intravenous (IV) administration of antibiotics. Primary treatment failure was defined as the presence of fever, abdominal pain, and turbid peritoneal dialysate, with a total peritoneal WBC count greater than 50% of the pre-treatment value after 3 days of treatment using the combination of meropenem with tobramycin or vancomycin. “Secondary cure” refers to cure after adjustment to the antibiotic regimen or change to second-line antibiotics in patients with primary treatment failure. Relapse was defined as recurrence of peritonitis with the same micro-organism within 28 days of clearing of the initial peritonitis episode and cessation of antibiotic therapy.

Treatment regimen
Patients who fulfilled the entry criteria received meropenem 0.5 g IV twice daily, plus tobramycin 15 mg IP in every dialysis bag for the first 7 days, and meropenem 0.5 g IV twice daily, plus vancomycin 8 mg/kg IP in every bag during the next 7 days, after a 1-g initial loading dose. Removal of the peritoneal dialysis catheter was considered when the dialysate bacterial culture revealed *Pseudomonas* species, fungal infection, tuberculosis, or vancomycin-resistant enterococci.

Monitoring
The duration of follow-up was 42 days. Before starting treatment and at days 1, 3, 5, 7, 10, 14, and 28 after the initiation of treatment, total and differential WBC counts were measured in peritoneal fluid. At days 0, 3, 7, 10, 14, and 28 after the initiation of treatment, bacterial and fungal cultures of fresh peritoneal effluent were performed. Complete blood count and liver and renal function tests were performed before and at 14 and 42 days after the initiation of treatment.

Statistical analysis
Numerical data are reported as mean ± standard deviation.

Results
We recruited 36 CAPD patients with clinical evidence of peritonitis into the study. Table I shows the baseline demographic data and clinical parameters of the patients. Table II profiles the bacteria isolated from the peritoneal dialysis fluid of the patients.

Clinical outcome
The primary cure rate for MTV therapy was 94.4% (34/36). The primary cure rate for peritonitis caused

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Profile of the study patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.7±2.1</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>25/11</td>
</tr>
<tr>
<td>CAPD duration (months)</td>
<td>34.5±3.6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>60.7±1.5</td>
</tr>
<tr>
<td>Cause of renal failure</td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>Bacteria isolated from dialysate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive [n (%)]</td>
<td>17 (47.2)</td>
</tr>
<tr>
<td>MSSA</td>
<td>6</td>
</tr>
<tr>
<td>MSCNSA</td>
<td>3</td>
</tr>
<tr>
<td>MRCNSA</td>
<td>5</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>2</td>
</tr>
<tr>
<td>Aerobic gram-positive bacteria</td>
<td>1</td>
</tr>
<tr>
<td>Gram-negative [n (%)]</td>
<td>7 (19.5%)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>3</td>
</tr>
<tr>
<td>NFGNR</td>
<td>2</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>2</td>
</tr>
<tr>
<td>No growth [n (%)]</td>
<td>12 (33.3%)</td>
</tr>
</tbody>
</table>

MSSA = methicillin-sensitive *Staphylococcus aureus*; MSCNSA = methicillin-sensitive coagulase-negative *S. aureus*; MRCNSA = methicillin-resistant coagulase-negative *S. aureus*; NFGNR = non-fermenting gram-negative bacteria.
by gram-negative bacteria was 100% (7/7) and that for peritonitis caused by gram-positive bacteria was 88.2% (15/17). The primary cure rate for culture-negative peritonitis was 100% (12/12).

**Adverse effects**

No serious adverse effects were reported. Mild adverse effects in clinical practice were liver dysfunction (n = 1) and eosinophilia (n = 5).

**Discussion**

In the present study, we describe for the first time an excellent cure rate for treatment with meropenem and tobramycin in combination, followed by meropenem and vancomycin in combination, for peritonitis in CAPD patients.

The carbapenems have excellent activity *in vitro* against nearly all bacterial pathogens; the exceptions are *Stenotrophomonas*, methicillin-resistant staphylococci, and *Enterococcus faecium*. Imipenem has dose-related central nervous system side effects that are less frequent with meropenem. Currently, therefore, meropenem is more frequently used in clinical practice. In addition, because of the clinical and bacteriologic efficacy of meropenem, it is an important antimicrobial drug in the treatment of serious infections.

Previously, the rate of complete cure reported in several studies conducted to evaluate the efficacy of monotherapy with IP imipenem–cilastatin in the treatment of CAPD-associated peritonitis was better than 90% (6,7). Based on those data, IP imipenem–cilastatin was proposed as an effective single first-line antibiotic for the treatment of peritonitis in CAPD patients, and the pharmacokinetics of imipenem–cilastatin in CAPD patients were reported (8). Precise pharmacokinetics for meropenem in patients undergoing CAPD had not been reported until recently (9). On the basis of the information available on imipenem–cilastatin and on the relationship between imipenem–cilastatin and meropenem, we chose meropenem at 0.5 g twice daily in patients undergoing CAPD. In the present study, meropenem was used in combination therapy with tobramycin and vancomycin, producing a high cure rate of 94%.

Because routes of administration and drug combinations vary, comparing data between previous studies using imipenem–cilastatin and the present study is not easy. Recently, Leung *et al.* (10) reported that the complete cure rate using monotherapy with imipenem–cilastatin was 72.5%, an efficacy similar to that with the standard regimens of cefazolin plus ceftazidime or netilmicin. These differences in cure rate might reflect changes in organisms and increases in antibiotic-resistant bacteria during the last 10 years (11,12).

The recent spread of vancomycin-resistant *S. aureus* and *Enterococcus* spp. led the ISPD to recommend the use of cefazolin, a first-generation cephalosporin (5). This recommendation has been challenged because of the high frequency of methicillin-resistant *S. aureus* and coagulase-negative staphylococci (3) among CAPD patients—as found in the present study. Indeed, two groups have recently demonstrated that, because of a high susceptibility rate, vancomycin (as compared with first-generation cephalosporins) should be used for gram-positive infections, in conjunction with close monitoring of local epidemiology and drug concentrations (2,4).

In the present study, we used tobramycin during the first 7 days as an empirical regimen. In 2000, the ISPD recommended (5) avoiding aminoglycosides as first-line therapy in patients who have significant residual renal function, because aminoglycosides were associated with faster decline of residual renal function in CAPD patients (13). Based on that recommendation and the dose-dependent nephrotoxicity of tobramycin (14), our use of tobramycin was restricted to a short duration. However, in the present study, a high percentage of the organisms isolated were resistant to tobramycin, negating the combination of tobramycin and meropenem as first-line antibiotics for the treatment of peritonitis in CAPD.

In recent years, preservation of residual renal function in patients undergoing CAPD has been recognized to be associated with improved survival and better quality of life (15). In the present study, the effects of a single episode of peritonitis and the use of IP aminoglycosides on residual renal function were not examined in the longer term. In addition, evaluating decline in residual renal function is not easy, because factors such as frequency of peritonitis and presence of diabetes mellitus and obesity are associated with a more rapid decline in residual renal function (16). In this regard, a relatively longer observation period for decline in residual renal function is needed to continue evaluating this antimicrobial regimen. Also, we did not compare the efficacy of previous regimens—such as a combination
of first- and third-generation cephalosporins—with our present treatment for CAPD peritonitis. A comparative, prospective, and randomized study between the traditional treatment and our new regimen of meropenem and vancomycin is required.

**Conclusions**

Treatment with IV meropenem plus IP tobramycin for the first 7 days, followed by IV meropenem plus IP vancomycin for the next 7 days is effective for CAPD peritonitis and has few adverse effects.

**References**


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