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Research Article

Meropenem Plus Tobramycin Followed by Meropenem Plus Vancomycin for Treating Peritoneal Dialysis-Related Peritonitis ---Single Center Experience---

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Abstract

Background: The microbial composition of peritoneal dialysis (PD)-related peritonitis isolates is changing as patients become older and the prevalence of end-stage renal disease caused by diabetic nephropathy rapidly increases. Thus, prevention and treatment of peritonitis are still matters of great concern.

Methods: A single center prospective, simple randomized study was carried out with 105 patients. We divided them into the two groups as follows: 1) 53 patients with conventional treatment (CT) (intravenous cefmetazole sodium (CMZ) plus intraperitoneal tobramycin (TOB)); and 2) 52 patients treated with meropenem, toburamycin and vancomycin (MTV; intravenous meropenem (MEPM) plus intraperitoneal TOB/VCM).

Results: The primary response rate in the MTV and CT groups was 94% (47/50) and 86% (43/50), respectively, after 5 patients dropped out in each group. This difference was not significant. Complete cure rates in the two groups were 92% (46/50) and 74% (37/50), respectively (P = 0.03). MTV treatment is thus more effective for PD-associated peritonitis, especially that caused by Gram-positive cocci (P<0.001). Although the same tendency was observed for culture-negative cases, the difference did not achieve significance, probably because of the low number of cases. There were no significant reductions in residual renal function in either group.

Conclusions: We suggest that MEPM plus TOB followed by MEPM plus VCM for treating peritoneal dialysis-related peritonitis is effective as an empirical primary therapy, but should be changed to narrow spectrum antibiotics immediately on identifying the causative bacteria, with strict review of antibiotic dosage to minimize adverse effects.

Keywords: Meropenem; Peritonitis; Residual Renal Function; Vancomycin

Introduction

Peritonitis is a serious complication for patients on peritoneal dialysis (PD), and is the primary reason for switching from PD to hemodialysis (HD) [1]. Appropriate use of antibiotics remains central to the treatment of peritonitis. The International Society for Peritoneal Dialysis (ISPD) published guidelines in 2000 [2] which were updated in 2005 [3]. Alternatively, first generation cephalosporin plus aminoglycosides can be immediately applied empirically while awaiting the results of PD drainage culture [4]. The microbial make-up of PD-related peritonitis has changed over the past 10 years as patients have become older and the prevalence of end-stage renal disease caused by diabetic nephropathy has rapidly increased [5]. In most published papers on this subject, the frequency of cases attributable to *coagulase-negative staphylococcus* (CNS) has decreased markedly over the

last decade or more, while the incidence of *Staphylococcus aureus* and CNS requires increased use of vancomycin hydrochloride (VCM). Thus, prevention and treatment of peritonitis are still matters of great concern [6,7]. With increased use of PD in our hospital, the number of patients with recurrence or biofilm build-up unresponsive to conventional therapy (intravenous (i.v.) cefmetazole sodium (CMZ) + intraperitoneal (i.p.) tobramycin (TOB) has also increased [8]. The ISPD committee recommended a center-specific selection of empiric therapy, dependent on the history of sensitivities of organisms causing peritonitis. In addition, the committee stated that Gram-positive organisms may be covered by vancomycin or a cephalosporin, and Gram-negative organisms by a third-generation cephalosporin or aminoglycoside [3]. To deal with these, it is necessary 1) to treat for both Gram-positive cocci (GPC) and Gram-negative rods (GNR) in empirical therapy of CAPD-related peritonitis; 2) to consider recent increases in the occurrence of MRCNS (*methicilin-resistant* CNS) as the cause of peritonitis; and, 3) to test whether in the absence of improvement by conventional therapy with i.v. CMZ and i.p. TOB, i.v. meropenem (MEPM) and i.p. VCM may be of benefit [8]. The aim of the present study was therefore to compare i.v. MEPM plus i.p. TOB/VCM with conventional therapy in terms of clinical efficacy and safety.

Methods

Subjects

All stable CAPD patients aged 18 or older in our dialysis center who had developed clinical evidence of PD-related peritonitis were eligible for the study. PD-related peritonitis was diagnosed when abdominal pain and cloudy peritoneal dialysis effluent (PDE) occurred with or without fever, and when the peritoneal white blood cell (WBC) count was >100/mm3 with >50% neutrophils. Informed consent was obtained from each patient. This study was approved by the Ethical Committee of Saitama Medical University.

Exclusion criteria

Patients who had known hypersensitivity to cephalosporins, aminoglycosides, VCM, or carbapenems, suspected fungal or tuberculous peritonitis, relapsing/recurrent peritonitis (i.e. an episode of peritonitis within 4 weeks of apparent recovery and cessation of antibiotic treatment after a previous episode of peritonitis), or active exit-site infection were excluded from the study.

Study design

This was a single center prospective, simple randomized and open-blind study in stable CAPD patients attending the Department of Nephrology, Saitama Medical University. Randomization was carried out by a computer-generated randomization table. After simple randomization was done for 105 patients, we divided them into two groups of 53 and 52 patients each as follows: 1) conventional treatment group (CT) (i.v. CMZ plus i.p. TOB), 2) meropenem, toburamycin and vancomycin (MTV) group (i.v. MEPM plus i.p. TOB/VCM). Dialysis connection methodology was a double-bag system and a flush-before-fill was performed. More than 95% patients received CAPD on 1.0 to 1.5 L/exchange, 3 to 4 exchanges per day. Purulent drainage, even if this was the only sign, was taken as sufficient to indicate infection.

All patients participating in this study underwent a training protocol including learning aseptic technique with emphasis on proper hand washing, cleaning of the location for exchanges with avoidance of animal hair, dust-laden air, and fans.

Power calculations for determining the number of patients required to evaluate an outcome were not done, because this was originally intended to be a pilot study.

Treatment regimens

Patients who fulfilled the entry criteria were randomized to receive either CT or MTV as follows: Patients in the CT group received 1 g i.v. CMZ twice daily, plus 10 mg i.p. TOB per dialysis bag for the first 3 days, and then 0.5 g CMZ twice daily, plus 10 mg i.p. TOB per bag over the next 11 days. Patients in the MTV group received 0.5 g i.v. MEPM twice daily, plus 10 mg i.p. TOB in every dialysis bag for the first 7 days except for the nocturnal PD solution at day 7 (1 g i.p. VCM initial loading dose in the PD solution), and 0.5 g i.v. MEPM daily, plus i.p. 8 mg/kg VCM in the nocturnal PD solution over the next 7 days. We compared these two therapies over 2 weeks, and then followed the patients for 6 weeks after initiation of treatment. If peritonitis was improving, we continued the empirical therapy whether or not the culture s results were available after 1 week. Removal of the peritoneal dialysis catheter was considered when the dialysate bacterial culture revealed *Pseudomonas species* (e.g. *Pseudomonas aeruginosa*), or VCM-resistant enterococci (VRE). Concomitant serum and dialysate levels of antibiotics were not measured.

Definitions of cure, relapse and recurrence.

Complete cure was defined as complete resolution of signs and symptoms of peritonitis, PDE WBC count <100/ml and no further episodes of peritonitis within 4 weeks of cessation of antibiotic treatment. Primary treatment failure was defined as the presence of fever, abdominal pain, and turbid peritoneal dialysate, with a total peritoneal WBC count >50% of the pre-treatment value 3 days after

treatment. Usually the decision was made to remove the catheter or antibiotics were changed at this point. Primary response was defined as resolution of abdominal pain, clearing of dialysate, and PDE WBC count <100/ml on day 10 with antibiotics alone. Relapse was defined as an episode occurring within 4 weeks of completion of therapy for a prior episode with the same organism, or after one sterile episode. Recurrence was defined as an episode occurring within 4 weeks of completion of therapy for a prior episode but with a different organism, or after one sterile episode. The catheter was removed when there was a lack of improvement or empirical suspicion of biofilm formation, which was validated by electron microscopy [9].

Monitoring

The duration of follow-up was 6 weeks. Before starting treatment and on days 1, 3, 5, 7, 10, 14, 28, and 42 after the initiation of treatment, WBC counts in peritoneal fluid were recorded. Complete blood counts, transaminase, and 24-hour urine volume were measured on days 1, 14, and 42 after the initiation of treatment. On days 0, 3, 7, 10, 14 and 28 after the initiation of treatment, bacterial and fungal cultures of fresh peritoneal effluent were performed. Therapeutic safety parameters were set as follows: Liver functional impairment was defined as transaminase (AST/ALT) levels greater than twice those at initiation of treatment. Progression of renal dysfunction was defined as production of maximally half the normal 24-hour urine volume. Bone marrow suppression was defined as WBC <3000/μl, or platelets (Plt) <100×10³/μl. Allergy was defined as drug-related eruptions or eosinophils at > 500/μl. Blood-culture bottles were directly injected with 10 ml of effluent because equipment for centrifuging large amounts of fluid was not available.

Assessment of residual renal function (RRF)

Serum and urinary creatinine, and 24-hour urine volumes measured on days 1, 14, and 42 after entry into the study in complete cure patients (cure effects by the assigned i.p or i.v. administration of each antibiotic s, without having to change to other antibiotics) were recorded for assessment of RRF. Urine volume and the mean of urea and creatinine clearance normalized to 1.73 body surface area (BSA) (nCrCl) were measured. The effects of the two treatment regimens on 24-hour urine volumes on days 1, 14, and 42 after the start of treatment were also compared in these patients.

Statistical analysis

Statistical analysis was performed using StatView-J5.0 (SAS Institute Inc.). Numerical data are given as mean ± standard deviation (SD). The paired t-test was used to compare mean values before and after therapy in each group. Means between groups were compared with the unpaired t-test or contingency table analytical statistics. One-way repeated measures analysis of variance (ANOVA) followed by Newman Kuels testing was used for comparison of time-dependent data. A P value <0.05 was considered statistically significant.

Results

Stable CAPD patients with clinical evidence of peritonitis were recruited into the study between July 11, 2002 and November 5, 2005 (n=105). The study was performed through December 16, 2005. The patient flow-chart is shown in Figure 1. The number of patients presenting with peritonitis was 137 and the number of patients eligible for the study was 115. Of these, 105 agreed to participate, 53 randomized to the CT group, and the remaining 52 to the MTV group. The baseline demographic data and clinical parameters of the two groups are shown in Table 1. There were no significant differences between them in age, frequency of diabetes mellitus, duration of PD, body weight, number of peritonitis episodes, body temperature, urine production and water excretion, PD-WBC count, peripheral WBC count, serum CRP (C-reactive protein), or serum albumin. Two in the CT group and 3 in the MTV group dropped out because of leaving hospital or of their own volition. No patient died in either arm during the 6 weeks of follow up.
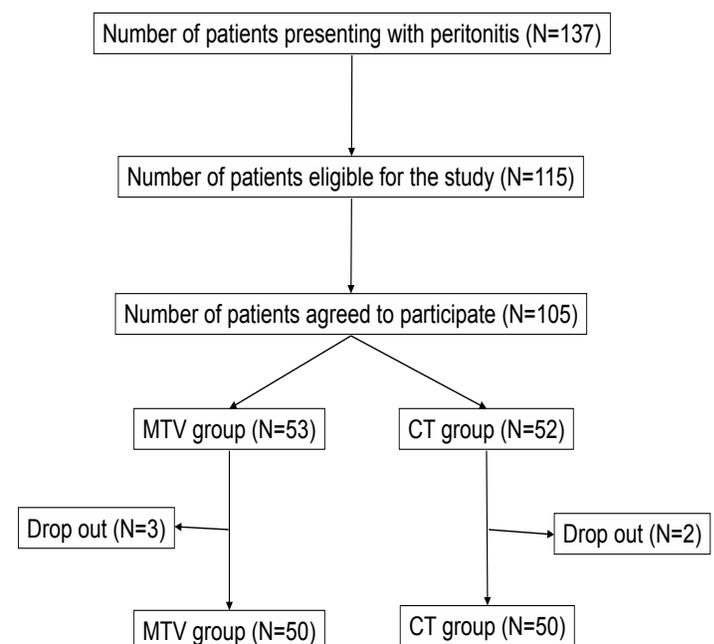

Figure 1. Flow chart for of patients in the study

Table 1. Baseline Demographic Data

|	CT group	MTV group	P value
Number of patients	53	52	
Age (years)	58.6 ± 10.4	61.3 ± 12.8	0.24
Sex male / female	38 / 15	37 / 15	
Duration of CAPD (months)	39.4 ± 43.2	32.5 ± 21.4	0.30
Body weight (kg)	57.9 ± 12.5	59.6 ± 9.3	0.43
DM* / non DM	18 / 35	19 / 33	0.67
History of prior peritonitis events (per patient)	1.2 ± 1.8	0.8 ± 1.0	0.19
Body temperature (°C)*	37.3 ± 0.8	37.1 ± 0.8	0.26
Urine volume (ml/day)	0∼1786	0∼1686	
Urine volume of patients without anuria (ml/day)	609 ± 431	576 ± 444	0.75
anuria (number of patients)	18	13	
oliguria (number of patients)	27	32	
Peritoneal WBC (/μl)	171∼22500 (3574 ± 4872)	131∼40300 (3897 ± 6131)	0.77
WBC (/μl)	9721 ± 3918	8410 ± 3737	0.08
CRP (mg/dl)	4.49 ± 3.4	3.9 ± 4.2	0.39
Alb (g/dl)	3.2 ± 0.5	3.1 ± 0.5	0.33
BUN (mg/dl)	56 ± 13	54 ± 15	0.67
sCr (mg/dl)	9.72 ± 2.98	8.75 ± 3.14	0.11

*DM: diabetes mellitus   (mean ± SD)
*°C = (F-32)x5/9
WBC: white cell blood count; CRP, C-reactive protein; Alb, albumin; BUN, blood urea nitrogen; sCr, serum creatinine.

Clinical Outcome

Clinical outcomes are shown in Figure 2. The primary response rate in the MTV and CT groups was 94% (47/50) and 86% (43/50), respectively (NS). The complete cure rates in the two groups were 92% (46/50) and 74% (37/50), respectively (P=0.03). Nine complete cure patients were among those who needed to change antibiotics in the CT group. The bacteria isolated from these patients were identified as *methicilin-resistant coagulase-negative staphylococcus* (MRCNS) in 3, *methicillin-sensitive staphylococcus aureus* (MSSA) in 2, *methicillin-resistant staphylococcus aureus* (MRSA) in one, *α–streptococcus* in one, *Bacteroides thetaiomicron* in one and no growth in the remaining one. There was only one complete cure patient who needed to change antibiotics in the MTV group. In that group, MRSA was isolated from the one patient, and then MSSA was isolated after recovery of the first episode of peritonitis (recurrent peritonitis). In contrast, there were 6 cases of relapsing/recurrent peritonitis in the CT group. There was one relapsing peritonitis with isolated MRCNS and 5 unidentified. The organisms in the relapsing/recurrent patients in the CT group were MRCNS in 2 cases, both *Bacteroides thetaiomicron* and NF-GNR in one, but no growth in the remaining three. There were no significant differences between the 2 groups in the incidence of relapsing/recurrent peritonitis. The catheter had to be removed in 7 CT group patients but only in 3 MTV (1 *Pseudomonas aeruginosa*, 1 MRCNS, 1 *Aeromonas spp.*) and intractable peritonitis in the remaining 4 in the CT group [culture negative]; 3 *Pseudomonas aeruginosa* in the MTV group). There were no significant differences in incidence of catheter removal between the 2 groups.
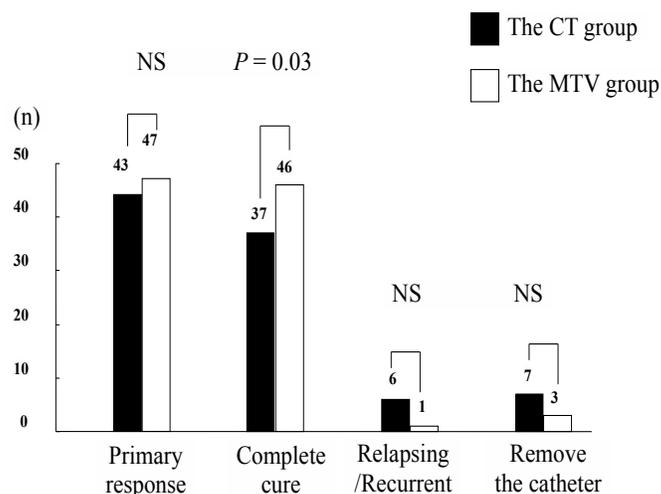
Figure 2. Clinical outcome
Complete cure rates are significantly different between the two groups (p=0.03), although incidences of relapsing/recurrent responses and frequency of removal of the catheter were not significantly different.

Isolated bacteria

The profile of bacteria isolated from the PDE of patients in the 2 treatment groups is shown in Table 2. There were

46 Gram-positive bacteria, 32 Gram-negative, and 22 culture-negative. 40% of isolates in both patient groups were Gram-positive bacteria, the majority CNS (20), of which 80% were MRCNS [16-20].

Table 2. Profile of bacteria isolated from the PDE

Bacterial isolates	Number of patients of the CT group (%)	Number of patients of the MTV group (%)
Gram-positive isolates	23 (46%)	23 (46%)
MRCNS	8	8
MSCNS	0	4
α-Streptococcus	7	1
MSSA	4	5
MRSA	2	2
Corynebacterium spp.	1	1
γ-Streptococcus	1	0
Enterococcus faecium	0	1
Propionibacterium spp.	0	1
Gram-negative isolates	16 (32%)	16 (32%)
NF-GNR	0	5
Klebsiella pneumoniae	4	3
Bacteroides thetaiomicron	2	0
Escherichia coli	1	0
Klebsiella oxytoca	1	0
Serratia marcescens	1	0
Bacteroides vulgatus	1	0
Bacteroides fragilis	1	0
Acinetobacter baumanni	1	2
Acinetobacter spp.	0	2
pseudomonas aeruginosa	1	3
Enterobacter cloacae	1	0
Aeromonas spp.	1	1
Culture negative	11 (22%)	11 (22%)
Total	50	50

MRCNS : *methicilin-resistant coagulase-negative staphylococcus*
MSCNS : *methicilin-sensitive coagulase-negative staphylococcus*
MSSA : *methicillin-sensitive staphylococcus aureus*
MRSA : *methicillin--resistant staphylococcus aureus*
NF-GNR : *non-fermenting gram-negative rod*

Changes in RRF

Figure 3a shows serial changes in RRF of patients with peritonitis completely cured without changing antibiotics who had RRF > 1 mL/min before entry into the study (n=45, of whom 17 were in the CT group and 28 in the MTV group). There were no significant differences within or between groups. Serial changes in 24-hour urine volume of the patients completely cured without changing antibiotics in the 2 treatment groups having a volume of > 100 mL were examined (n=54 before entry into the study, of whom 20 were in the CT group, and 34 in the MTV group). Figure 3b shows serial changes in urine volume in PD patients of the two groups with peritonitis successfully treated. The 24-hour urine volume in both treatment groups on day 1 was similar (637 ± 534 mL in the CT group vs. 609 ± 466 mL in the MTV group). After completion of i.v. and i.p. antibiotic treatment on day 14, 24-hour urine volume in both groups decreased compared to the baseline values. They dropped to 522 ± 433 mL and 400 ± 336 mL in the CT and MTV groups respectively. This represents a percentage decrease in the 24-hour urine volume in the CT and MTV groups of 18% and 34%, respectively (P = 0.89). By day 42, 24-hour urine production had returned to near-baseline values in both groups (608 ± 575 mL for the CT group and 664 ± 433 for the MTV group). There were no significant differences between the 2 groups.
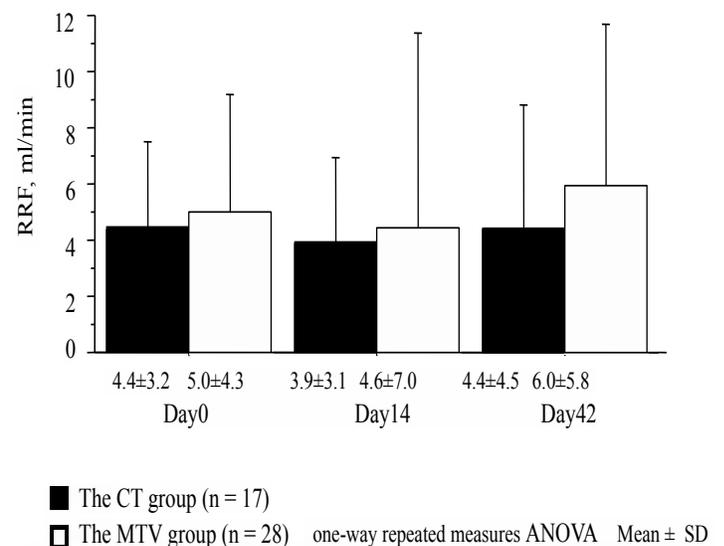

Figure 3a. Serial change in RRF of PD patients with peritonitis successfully treated in patients of the two groups having had RRF > 1 mL/min before entry into the study.
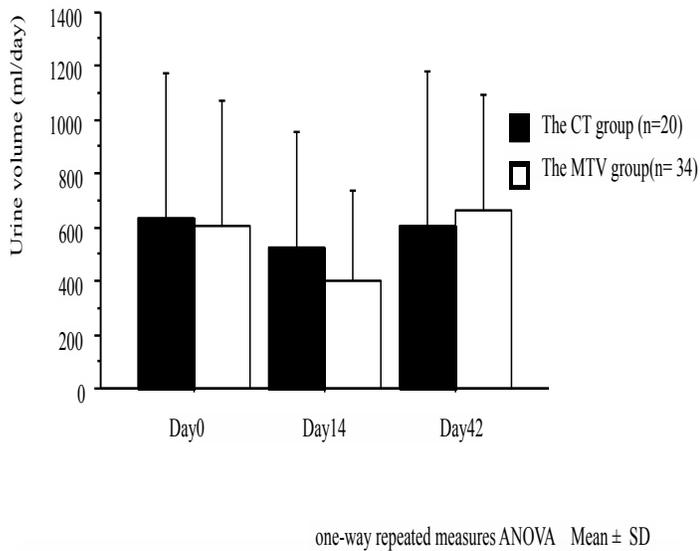There were no significant differences within or between groups.

Figure 3b. Serial change in urine volume of PD patients with peritonitis successfully treated in patients of the two groups

Adverse effects

Adverse events noted in the CT group were progression of renal dysfunction in 16 patients and allergy in 2. In the MTV group, two patients suffered liver function impairment, 5 had progression of renal dysfunction, and 1 allergy. However, none of these adverse effects was serious. Antibiotic treatment could be continued in the 2 cases of liver function impairment in the MTV group, and liver function returned to baseline after their discontinuation due to patients´primary responses, and complete cure.

Discussion

From the present study, we conclude that, first; MTV treatment is significantly better than conventional therapy for PD-associated peritonitis in terms of complete cure rates. Second, neither treatment caused any significant decrease in RRF.

The carbapenems have excellent activity in vitro against nearly all bacterial pathogens, except for *Stenotrophomonas, methicillin-resistant staphylococci*, and *Enterococcus faecium*. Previously, the efficacy of monotherapy using i.p. imipenem-cilastatin (IPM/CS) had been reported in several studies of CAPD-related peritonitis, yielding a cure rate >90% [10,11]. Based on those data, i.p. IPM/CS was proposed as an effective single first-line antibiotic for the treatment of peritonitis in CAPD patients. An additional advantage was knowledge of the pharmacokinetics of IPM/CS in CAPD patients [12]. Thus, by employing precise pharmacokinetics of meropenem (MEPM) in patients undergoing CAPD, Thalhammer et al. could recommend once-daily administration of 0.5 - 1.0 g [13]. In that study, MEPM had

been selected because of its lesser side effects in the central nervous system, as seen, for example, for convulsions with carbapenems. On the basis of the information available on IPM/CS, and the relationship between IPM/CS and MEPM, here we elected to use 0.5 g of MEPM twice daily until day 7 and then 0.5 g once daily from day 8 to 14 in patients undergoing CAPD. In addition, we chose i.p. TOB, and changed to VCM on day 7, because we considered a Gram-negative rod infection by CNS likely. Despite the general success of this primary care approach and excellent sensitivity of detected bacteria to the agents employed, we still had refractory cases involving other bacteria. When this occurred, we assumed the presence of MRSA or certain resistant MRCNS and therefore changed from i.p. TOB to i.p. VCM on day 7. Previously we reported that i.v. MEPM plus i.p. TOB followed by MEPM plus VCM resulted in a high cure rate of 94% for treating peritonitis in patients on CAPD [8]. Because routine use of the wide spectrum antibiotics carbapenems together with VCM might strongly select for resistance, this treatment cannot be applied to all cases. Thus, the emergence of *vancomycin-resistant enterococci* has been reported [14,15]. However, based on our previous study of 4 refractory patients under CT who responded to the change of antibiotics to i.v. MEPM plus i.p. VCM [8], we hypothesized that starting treatment with MTV before bacterial identification in CAPD-associated peritonitis, and then changing to a more specific regimen as soon as possible thereafter, could provide good primary care with lower risk of development of resistance. Leung et al. [16] had reported a complete cure rate of 72.5% on monotherapy with IPM/CS, similar to the standard regimens cefazolin (CEZ) and ceftazidime (CAZ), or netilmycin. These differences in cure rates might reflect changes in causative organisms and increases in antibiotic resistance over the last 10 years [17,18]. In fact, it was the recent spread of vancomycin-resistant *Staphylococcus aureus* (VRSA) and *Enterococcus spp*. that led the ISPD to recommend the use of CEZ, a first generation cephalosporin, instead [3]. This recommendation has now been challenged because of the high frequency of MRSA and CNS among CAPD patients, as found in the present study [6]. Indeed, based on close monitoring of local and serum drug concentrations, two groups have recently demonstrated that VCM should be used for Gram-positive infections, because of their greater susceptibility to this agent than to first-generation cephalosporins [4,7]. In the present study, we used TOB during the first 7 days as an empirical regimen. In 2005, the ISPD recommended avoiding aminoglycosides as first-line therapy in patients who have significant RRF [1], because use of these agents was associated with more rapid RRF decline in CAPD patients [19]. Based on that recommendation and the dose-dependent nephrotoxicity of TOB [20], we restricted our use of this agent to a short duration because preservation of RRF in patients undergoing CAPD is recognized to be associated with improved survival and better quality of life [21]. In the present study, there was no significant reduction in RRF after 14 days' antibiotic treatment in peritonitis

patients who were completely cured without changing antibiotics. While urine volume in the MTV group was decreased 14 days after the onset of peritonitis, there was good recovery by day 42. Persistence of increased levels of proinflammatory cytokines and growth factors at least 6 weeks after apparent clinical remission of peritonitis has been reported in CAPD patients [22]. Evaluating declines in RRF is not straightforward, because such factors as frequency of peritonitis, presence of diabetes mellitus and obesity as well as the above-mentioned total body water and amount of excretion are all associated with a more rapid decline in RRF [23].

Concerning the dose-regimen, the ISPD recommends intermittent or persistent administration i.p. [3]. The two antibiotics TOB and VCM are referred to in these guidelines, as used in the present study. In addition, CMZ and MEPM are known to show good intraperitoneal migration on i.v. administration. The ISPD recommends TOB either at a daily dose of 0.6 mg/kg or a loading dose of 8 mg, followed by maintenance doses of 4 mg per one-liter bag, and to increase the dose by 25% in cases where urine volume >100 ml per day is recorded. In the present study, 10 mg per bag of TOB was administered independently of body weight, to achieve the same 24-hour dose as given in conventional therapy. Baker et al. showed that there were no significant differences in the rate of decline of RRF in CAPD patients treated with or without gentamicin for CAPD peritonitis (24). Although it is well-established that aminoglycosides are nephrotoxic, this is dose dependent [20], so intermittent administration, as pursued here, may be advantageous due to decreased risk of nephrotoxicity.

The recommended dose of VCM is also either 15 - 30 mg/kg daily for 5 to 7 days (intermittent administration) or a loading dose of 1,000 mg followed by maintenance doses of 25 mg per one-liter bag (persistent administration) again with a recommended increase of 25% for urine production >100 ml per day. In the present study, we selected a loading dose of 1,000 mg, but maintenance doses of 8 mg/kg (a total of the relatively large dose of 0.5g) with administration at night. For such intermittent administration regimens, it is assumed that antibiotic levels are maintained for at least a minimum of 6 hours. However, because of the temporary reduction in urine volume, more precise studies of optimal maintenance doses and dosing intervals for maximizing VCM efficacy are required.

Before drawing definitive conclusions, we have to consider several points. First, the dose of antibiotics should be evaluated cautiously, because temporary oliguria in the MTV group was found. Second, this is not a pure randomized study because the prevalence of bacteria causing PD peritonitis in the 2 groups was not matched. In addition, the problems with culture-negative cases were ignored. Third, changes from TOB to VCM one week after starting therapy seem to be empiric. These issues need to be considered when deciding whether to apply MTV treatment for patients suffering from PD peritonitis.

In conclusion, from the present study, it is suggested that MEPM plus TOB followed by MEPM plus VCM for treating peritoneal dialysis-related peritonitis is effective as an empirical primary therapy. However, the initial treatment should be changed to narrow spectrum antibiotics immediately on identifying the causative bacteria, with strict review of antibiotic dosage to minimize adverse effects.

Disclosures

None.

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