Cefazolin plus netilmicin versus cefazolin plus ceftazidime for treating CAPD peritonitis: Effect on residual renal function

SING LEUNG LAI, SUK WAI CHENG, FLORA NG, SUK YI NG, KIT MUI WAN, TERENCE YIP, KAI CHUNG TSE, MAN FAI LAM, KAR NENG LAI, and WAI KHE LO

Division of Nephrology, University Department of Medicine, Tung Wah Hospital, Hong Kong SAR, People's Republic of China

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Background. The International Society for Peritoneal Dialysis (ISPD) treatment guidelines for continuous ambulatory peritoneal dialysis (CAPD) peritonitis 2000 recommended the use of cefazolin plus ceftazidime as the initial empirical therapy in patients with residual renal function (RRF). However, this treatment regimen has not been compared with the conventional regimen of cefazolin plus netilmicin in prospective, randomized controlled trials.

Methods. Stable CAPD patients who developed clinical evidence of peritonitis were randomized to receive intraperitoneal (i.p.) cefazolin plus netilmicin or cefazolin plus ceftazidime once daily in the long dwell for 14 days. For patients with RRF (>1 mL/minute) before entry into the study (N = 50), RRF and 24-hour urine volume were measured at days 1, 14, and 42 after commencement of i.p. antibiotic treatment.

Results. One hundred and two patients were recruited into the study. The primary cure rates of i.p. cefazolin plus netilmicin and cefazolin plus ceftazidime were 66.7% and 64.7%, respectively. The overall cure rate for the 2 treatment regimens was 82.3% for both. Seven patients (14%) from each treatment group required removal of the dialysis catheters due to treatment failure. Relapse of peritonitis occurred in 2 patients (4%) in both treatment groups. Thirty-six patients with RRF at baseline achieved primary cure of their peritonitis by the assigned antibiotics. In this subgroup of patients, their RRF and daily urine volume showed significant reduction at day 14 and returned to near baseline values at day 42. The degree of reduction in RRF and urine volume did not differ significantly between the patients treated with cefazolin plus netilmicin and cefazolin plus ceftazidime.

Conclusion. Intraperitoneal cefazolin plus netilmicin and cefazolin plus ceftazidime have similar efficacy as empirical treatment for CAPD peritonitis. In CAPD patients with RRF, significant but reversible reduction in RRF and 24-hour urine volume could occur after an episode of peritonitis, despite successful treatment by i.p. antibiotics. The effect of i.p. cefazolin plus netilmicin, or i.p. cefazolin plus ceftazidime on RRF in CAPD patients with peritonitis does not appear to be different. Our findings do not support the routine use of cefazolin and ceftazidime as the empirical treatment for CAPD peritonitis.

In recent years, it has been recognized that preservation of residual renal function (RRF) in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) is associated with improved survival and better quality of life [1, 2]. The factors that influence the rate of loss of RRF in CAPD patients have not been completely elucidated. It has been suggested that higher rate of peritonitis, the presence of diabetes mellitus, and obesity are associated with a more rapid loss of RRF [3–5]. It has also been reported that CAPD patients who have been treated with aminoglycosides have a faster rate of decline of RRF [4, 6]. In view of the potential nephrotoxic effect of aminoglycosides, the International Society for Peritoneal Dialysis (ISPD) guidelines for the treatment of CAPD peritonitis 2000 recommended that a first and a third generation cephalosporin, such as cefazolin plus ceftazidime, be used as the initial empirical antibiotic treatment for CAPD-related peritonitis, and that the conventional regimen of cefazolin plus netilmicin be avoided in patients with RRF [7].

However, it should be noted that the clinical efficacy of cefazolin plus ceftazidime for the treatment of CAPD peritonitis has not been compared with cefazolin plus netilmicin in prospective randomized clinical trials. There is also a lack of prospective data regarding the effect of a single episode of peritonitis and the use of intraperitoneal (i.p.) aminoglycosides on RRF in CAPD patients.

The aim of this study was to compare i.p. cefazolin plus netilmicin versus i.p. cefazolin plus ceftazidime for the treatment of CAPD peritonitis in terms of their clinical efficacy and their effect on RRF.

METHODS

Study design

This study was a prospective, randomized, open-labeled study in stable CAPD patients in a single dialysis
center of a university teaching hospital. The randomization was done by computer generated randomization table. The study protocol was approved by the Hospital Ethical Committee for Clinical Research.

**Subjects**

All stable CAPD patients aged 18 or older in the dialysis center who had developed clinical evidence of peritonitis were eligible for the study. Peritonitis was diagnosed when abdominal pain and cloudy peritoneal dialysis fluid (PDF) occurred with or without fever, and when peritoneal white cell count (WBC) count was >100/mm³ with >50% neutrophils. Informed consent was obtained from each patient. The flow of patients in the study is shown in Figure 1.

**Exclusion criteria**

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

**Definitions**

Cure is defined as complete resolution of signs and symptoms of peritonitis with negative PDF cultures and no further episodes of peritonitis within 28 days following the cessation of antibiotic treatment. Primary cure refers to cure by the assigned i.p. antibiotics. Primary treatment failure is defined as the presence of fever, abdominal pain, and turbid peritoneal dialysate, and if the total peritoneal WBC counts is >50% of the pretreatment values after 3 days of treatment by the assigned antibiotics. Secondary cure refers to cure after adjustment of antibiotics or changing to second line antibiotics in patients with primary treatment failure. Secondary treatment failure is defined as recurrence of peritonitis with the same microorganism within 28 days of clearing of the initial peritonitis episode and cessation of antibiotic therapy.

**Treatment regimen**

Patients who fulfilled the entry criteria were randomized to receive either i.p. cefazolin plus netilmicin or i.p. cefazolin plus ceftazidime, given once daily in the long dwell. The dosage of the i.p. antibiotics were as follows: cefazolin (1 g per 2 L PDF); netilmicin (0.6 mg/kg body weight per 2 L PDF); and ceftazidime (1 g per 2 L PDF). The duration of treatment was 14 days. If the peritonitis failed to respond to the assigned i.p. antibiotics by day 3 (primary treatment failure), the antibiotics would be adjusted according to the PDF bacterial culture results or be changed to second line antibiotics (vancomycin plus amikacin) if the PDF bacterial cultures were negative. Removal of the peritoneal dialysis catheters would be considered in patients with primary treatment failure whose peritonitis failed to improve after adjusting the i.p. antibiotic regimens for 3 to 5 days (secondary treatment failure).

**Monitoring**

The duration of follow-up was 42 days. Before starting treatment and at days 1, 3, 5, 7, 10, 14, 28 after the initiation of treatment, peritoneal fluid total plus differential WBC count were measured. 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, liver and renal function tests were measured before and at 14 and 42 days after the initiation of treatment.

**Measurement of RRF**

For patients with RRF of greater than 1 mL/min as determined at the last routine follow-up before entry into the study, their RRF and daily urine output were determined at days 1, 14, and 42 after entry into study. Estimated RRF was calculated as the mean of creatinine
Statistical analysis

after the initiation of treatment were compared.

on RRF and 24-hour urine volume at days 1, 14, and 42
to further analysis. The effect of the 2 treatment regimens
peritonitis by the assigned i.p. antibiotics were subjected
1mL/min and who had achieved primary cure of their
RRF, a subgroup of patients whose RRF was greater than
plus netilmicin versus i.p. cefazolin plus ceftazidime on

Data analysis

In order to directly compare the effect of i.p. cefazolin
plus netilmicin versus i.p. cefazolin plus ceftazidime on
RRF, a subgroup of patients whose RRF was greater than
1 mL/min and who had achieved primary cure of their
peritonitis by the assigned i.p. antibiotics were subjected
to further analysis. The effect of the 2 treatment regimens
on RRF and 24-hour urine volume at days 1, 14, and 42
after the initiation of treatment were compared.

Statistical analysis

Statistical analysis was performed using SPSS (SPSS,
Chicago, IL, USA) statistical software. Numerical
data are given as mean ± SD. Means between groups were
compared with Student t test and Mann-Whitney test
when appropriate. Percentages were compared by means
of Fisher exact test. A P value equal to or less than 0.05
is considered statistically significant.

RESULTS

One hundred and two stable CAPD patients with clinical
evidence of peritonitis were recruited into the study
from October 2002 to October 2004. Fifty-one patients
were randomized to receive i.p. cefazolin plus netilmicin,
while the other 51 patients were randomized to receive
i.p. cefazolin plus ceftazidime. The baseline demographic
data and clinical parameters of the 2 treatment groups
are shown in Table 1. The 2 groups of patients were com-
parable with respect to age, sex ratio, duration of CAPD,
body weight, causes of renal failure, and peritoneal WBC
count on presentation. The profile of bacterial isolates
from the PDF of the patients in the 2 treatment groups is
summarized in Table 2.

Clinical outcome

The primary cure rate of the assigned antibiotic regi-
men for the cefazolin plus netilmicin and the cefazolin
plus ceftazidime groups was 66.7% and 64.7%, respec-
tively (P = 0.84). The overall cure rate, after allowing
for adjustment of i.p. antibiotic regimens, of the cefa-
zolin plus netilmicin and the cefazolin plus ceftazidime
groups was 82.3% for both. Seven patients (14%) from
each of the 2 treatment groups failed to respond to the i.p.
antibiotic treatment and required removal of their peri-
toneal dialysis catheters. The interval between presenta-
tion and catheter removal in the cefazolin plus netilmicin
group and cefazolin plus ceftazidime group was 7.3 ±
1.1 days and 7.1 ± 1.1 days, respectively. Relapse of per-
tonitis occurred in 2 patients (4%) from both treatment
groups. For peritonitis caused by Gram-positive bacte-
ria, the primary cure rate in the cefazolin plus netilmicin
and cefazolin plus ceftazidime groups was 73% and 65%,
respectively (P = 0.07), whereas for peritonitis caused
by Gram-negative bacteria, the primary cure rate in the
cefazolin plus netilmicin and cefazolin plus ceftazidime
groups was 56% and 54%, respectively (P = 0.93). The
primary cure rate for culture negative peritonitis was 73%-
and 75% for the cefazolin plus netilmicin and cefazolin
plus ceftazidime groups, respectively (P = 1).

Residual renal function

Fifty patients had RRF of >1 mL/min before entry
into the study. Thirty-six out of these 50 patients achieved

| Table 1. Demographic data and clinical parameters of the study population |
|-----------------|-----------------|-----------------|-----|
|                 | Cefazolin + Netilmicin | Cefazolin + Ceftazidime | P value |
| Number of patients | 51               | 51               | 0.17 |
| Age years         | 63.7 ± 14.6 (26–89) | 66.7 ± 12.2 (30–90) | 0.55 |
| Sex male:female   | 1:3:1            | 1:3:1            | 0.93 |
| Duration of CAPD months | 44.1 ± 40.5 (3–157) | 46.3 ± 53.3 (1–240) | 0.07 |
| Body weight kg    | 59.6 ± 14.1 (35–89.3) | 58.6 ± 9.6 (39.6–79) | 0.28 |
| Cause of renal failure |
| Glomerulonephritis | 16               | 13               | 0.43 |
| Diabetic nephropathy | 17               | 13               | 0.11 |
| Hypertensive nephropathy | 3               | 6               | 0.62 |
| Polycystic kidney disease | 1               | 3               | 0.28 |
| Others/unknown   | 14               | 16               | 0.55 |
| Peritoneal WBC count (/mm³) on presentation with RRF >1 mL/min | 4715 ± 5188 (164–22100) | 3254 ± 3166 (150–13200) | 0.11 |
| Number of patients who have achieved primary cure | 24 (47%) | 26 (51%) | NS |

| Table 2. Profile of bacteria isolated from the PDF of patients treated with i.p. cefazolin plus netilmicin or cefazolin plus ceftazidime |
|-----------------|-----------------|-----------------|-----|
| Bacterial isolates | Cefazolin + Netilmicin | Cefazolin + Ceftazidime | P value |
| Gram-positive isolates | 22 (43%) | 26 (51%) | 0.43 |
| S. aureus; methicillin-sensitive coagulase negative S. aureus | 3 | 2 | |
| MSCNS | 3 | 3 | |
| MRSA | 0 | 1 | |
| MRCNS | 2 | 0 | |
| Streptococcus species | 11 | 13 | 0.28 |
| Diphtheroid | 2 | 6 | |
| Bacillus | 1 | 1 | 0.81 |
| Gram-negative isolates | 18 (35%) | 13 (25%) | 0.81 |
| Escherichia coli | 8 | 8 | |
| Klebsiella pneumoniae | 4 | 2 | |
| Pseudomonas species | 2 | 2 | |
| Acinetobacter species | 2 | 0 | |
| Others | 2 | 1 ||
| No growth | 11 (22%) | 12 (24%) | 0.81 |

Abbreviations are: MSSA, methicillin-sensitive Streptococcus aureus; MSCNS, methicillin-sensitive coagulase negative S. aureus; MRSA, methicillin-resistant S. aureus; MRCNS, methicillin-resistant coagulase negative S. aureus.

clearance and urea clearance from a 24-hour urine col-
lection. The first urine collection was started on day 0 and
completed on day 1.
primary cure of their peritonitis by the assigned antibiotic regimens. Eighteen patients were treated by cefazolin plus netilmicin, while the other 18 patients were treated by cefazolin plus ceftazidime. The baseline demographic data and clinical parameters of the 2 treatment groups are shown in Table 3. The 2 groups of patients were comparable with respect to age, sex ratio, duration of CAPD, and causes of renal failure. The profile of bacteria causing the peritonitis in the 2 treatment groups were also similar (Table 4).

Figure 2 shows the change of PDF total WBC count with time in the 2 treatment groups. The serial change in RRF of the patients in the 2 treatment groups is shown in Figure 3. The RRF of both treatment groups was similar on day 1 (4.16 ± 2.54 mL/min in the cefazolin plus netilmicin group vs. 3.90 ± 2.99 mL/min in the cefazolin plus ceftazidime group, \( P = 0.65 \)). After 14 days of i.p. antibiotic treatment, there was a marked reduction of RRF in both treatment groups. In the cefazolin plus netilmicin group, the RRF decreased from 4.16 ± 2.54 mL/min to 2.82 ± 2.58 mL/min (\( P < 0.001 \)). Similarly, the RRF of the patients in the cefazolin plus ceftazidime group decreased significantly from 3.90 ± 2.99 mL/min to 2.58 ± 2.08 mL/min (\( P = 0.018 \)). The percentage change in RRF in the cefazolin plus netilmicin and the cefazolin plus ceftazidime groups at day 14 were 32% and 34%, respectively (\( P = 0.24 \)). Four weeks later or at day 42, the RRF of both treatment groups had returned to values close to the baseline as at day 1 (4.25 ± 3.08 mL/min vs. 4.16 ± 2.54 mL/min (\( P = 0.79 \) for the cefazolin plus netilmicin group and 4.00 ± 2.71 mL/min vs. 3.90 ± 2.99 mL/min (\( P = 0.76 \) for the cefazolin plus ceftazidime group).

Figure 4 shows the serial change in 24-hour urine volume of the patients in the 2 treatment groups. The 24-hour urine volume in both treatment groups at day 1 was similar (924 ± 528 mL in the cefazolin plus netilmicin group vs. 895 ± 507 mL in the cefazolin plus ceftazidime group, \( P = 0.74 \)). After completion of i.p. antibiotic treatment at day 14, the 24-hour urine volume of patients in both treatment groups decreased significantly compared to the baseline values. In the cefazolin plus netilmicin group, the 24-hour urine volume dropped from 924 ±
528 mL to 487 ± 347 mL (P < 0.001), whereas in the cefazolin plus ceftazidime group, the 24-hour urine volume dropped from 895 ± 507 mL to 587 ± 385 mL (P = 0.001). The percentage change in the 24-hour urine volume in the cefazolin plus netilmicin and the cefazolin plus ceftazidime groups were 47% and 34%, respectively (P = 0.28). By day 42 after entry into the study, the 24-hour urine of both treatment groups had risen back to near baseline values as at day 1 (828 ± 510 mL vs. 924 ± 528 mL, P = 0.15, for the cefazolin plus netilmicin group and 799 ± 546 mL vs. 895 ± 507 mL, P = 0.39, for the cefazolin plus ceftazidime group).

DISCUSSION

In this study, we confirmed that i.p. cefazolin plus netilmicin and cefazolin plus ceftazidime have similar efficacy as empirical treatment for CAPD peritonitis. In addition, we observed that there was a significant, although reversible, reduction in RRF at day 14 after an episode of peritonitis, despite prompt response of the peritonitis to i.p. antibiotics. Lastly, we found that patients treated with i.p. cefazolin plus netilmicin or i.p. cefazolin plus ceftazidime had similar degree of reduction in RRF at day 14 after peritonitis.

The findings of our study provided confirmatory evidence that i.p. cefazolin plus netilmicin and i.p. cefazolin plus ceftazidime are equally effective as empirical treatment for CAPD peritonitis. These findings are to be expected because the antibacterial coverage of netilmicin and ceftazidime are similar. As a matter of fact, the main reason why the ISPD guidelines 2000 recommended the use of i.p. cefazolin plus ceftazidime instead of i.p. cefazolin plus netilmicin for the treatment of CAPD peritonitis is that the former combination is believed to be less nephrotoxic, not that it is more effective.

In our study, the significant reduction in RRF and 24-hour urine volume at the completion of 14 days’ i.p. antibiotic treatment in patients who had achieved primary cure of their peritonitis is noteworthy. This is because the peritonitis in these patients had responded promptly to the i.p. antibiotics such that their clinical signs and symptoms of peritonitis had resolved by day 3 after the initiation of treatment. One would therefore expect the peritonitis to have resolved completely and not to have any significant impact on RRF after 14 days of i.p. antibiotic treatment. The reason for the seemingly paradoxical deterioration in RRF despite prompt resolution of the peritonitis was not entirely clear. It has been reported that in CAPD patients, there was an active release of proinflammatory cytokines and growth factors through at least 6 weeks after apparent clinical remission of peritonitis [8]. It has also been shown that the levels of interleukin-6 and interleukin-8 in the PDF and plasma were significantly increased during peritonitis in patients on CAPD [9]. In cirrhotic patients with spontaneous bacterial peritonitis, it has been demonstrated that the plasma and ascitic fluid cytokine levels were significantly higher in those patients who developed renal impairment, suggesting that the inflammatory response to infection might be an important mechanism of renal impairment [10]. It is therefore plausible to postulate that bacterial peritonitis in CAPD patients could trigger off a systemic inflammatory reaction, which persists despite resolution of the clinical signs and symptoms of peritonitis. Such systemic inflammatory reaction, with its associated increased production of proinflammatory cytokines and growth factors, could adversely affect RRF. Other factors such as change in intravascular volume and filling pressures might also contribute to the decrease in RRF during peritonitis.

The reduction in RRF of our patients after bacterial peritonitis was not permanent but reversible. Both the RRF and the 24-hour urine volume of our patients returned to near baseline values at day 42 after an initial decrease at day 14. Our observation is echoed by the study of Dittrich et al, which showed that application of radiographic contrast media in CAPD patients also led to a significant but temporary decline in RRF [11]. In most previous studies, it has been suggested that higher rate of peritonitis is associated with a faster decline in RRF in CAPD patients [3, 4]. It is possible that although the acute effect of a single episode of bacterial peritonitis on RRF might be reversible, the cumulative effect of repeated episodes of peritonitis could lead to irreversible renal damage. It should be pointed out that the baseline RRF in our study was actually measured on day 1 after the patients had developed peritonitis and could have already started to decline. Nonetheless, because it was not possible to measure the RRF immediately before the...
patient develops peritonitis, the baseline RRF measured in our study is probably the best estimate of the genuine baseline RRF.

Gucket et al previously reported a prospective, randomized controlled trial of cefazolin plus netilmicin versus ceftazidime plus vancomycin in the treatment of CAPD peritonitis [12]. However, to the best of our knowledge, our study is the first one to compare the effect of cefazolin plus netilmicin and cefazolin plus ceftazidime on RRF in CAPD patients with bacterial peritonitis in a prospective, randomized fashion. Our results did not substantiate the notion that i.p. cefazolin plus netilmicin is more nephrotoxic than i.p. cefazolin plus ceftazidime in CAPD patients with RRF. In a recent study, Baker et al also showed that there were no significant differences in the rate of decline of RRF in CAPD patients treated with and without gentamicin for CAPD peritonitis [13]. Although it is well established that aminoglycosides are nephrotoxic, their nephrotoxicity is dose dependent [14, 15]. In our study, the dose of netilmicin used was relatively low. In addition, we had adopted the intermittent, once daily regimen of netilmicin administration, which has been shown to be less nephrotoxic [16]. These factors could have explained why in our study, i.p. cefazolin plus netilmicin was not more nephrotoxic than i.p. cefazolin plus ceftazidime. The routine use of a third generation cephalosporin for the treatment of peritonitis also has the potential disadvantage of encouraging the emergence of vancomycin-resistant enterococci [17] and extended-spectrum beta lactamase producing enterobacteriaceae [18]. Taken together, we would recommend the continue use of i.p. cefazolin plus netilmicin as the empirical treatment for CAPD peritonitis.

CONCLUSION

Intraperitoneal cefazolin plus netilmicin and i.p. cefazolin plus ceftazidime have similar efficacy as empirical treatment for CAPD peritonitis. A single episode of bacterial peritonitis, despite successful treatment by i.p. antibiotics, could result in a significant, although reversible, reduction in RRF. The degree of reduction in RRF appears to be similar in patients treated with i.p. cefazolin plus netilmicin or i.p. cefazolin plus ceftazidime. Our findings do not support the routine use of a first and a third generation cephalosporin in the empirical treatment of CAPD peritonitis. Further studies are warranted to elucidate the underlying mechanism for the reversible reduction in RRF after bacterial peritonitis despite apparent cure by i.p. antibiotics.

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Reprint requests to Dr. Sing Leung Lui, Division of Nephrology, University Department of Medicine, Tung Wah Hospital, 12, Po Yan Street, Sheung Wan, Hong Kong SAR, People's Republic of China. E-mail: slui@hku.hk

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