A prospective, randomized trial of two antibiotic regimens in the treatment of peritonitis in CAPD patients: teicoplanin plus tobramycin versus cephalothin plus tobramycin

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A multicentre, comparative, randomized study was performed to compare the efficacy and tolerability of two antibiotic regimens in the treatment of peritonitis in continuous ambulatory peritoneal dialysis (CAPD) patients: teicoplanin plus tobramycin versus cephalothin plus tobramycin. After informed consent had been obtained, 68 patients were randomized prospectively to receive either teicoplanin plus tobramycin or cephalothin plus tobramycin. Patients were followed throughout the study and for up to 4 weeks after the end of treatment, when clinical and microbiological parameters were assessed again. The incidence of clinical failure was 4.6 times higher in the cephalothin plus tobramycin group than in the teicoplanin plus tobramycin group (7/28 versus 2/37; P < 0.05). There was no significant difference in bacterial eradication between the two groups. Local and systemic tolerability were good for both regimens. The study shows that teicoplanin plus tobramycin is more effective than cephalothin plus tobramycin and might become a ‘first-line’ treatment for peritonitis in CAPD patients.

Introduction

Despite improvements in technology, peritonitis still remains the most frequent complication of continuous ambulatory peritoneal dialysis (CAPD), and strongly influences its long-term results, being the commonest cause of technique failure and hospitalization.1

Treatment of peritonitis is usually started before the result of dialysate culture is available, antibiotics being chosen as an ‘empirical’ first-line therapy active against the most frequent causative microorganisms. Gram-positive bacteria are the most often isolated,2 but the increasing prevalence of methicillin-resistant staphylococci limits the choice of appropriate antibiotics.

A recent update on the treatment of CAPD peritonitis recommends, as initial empirical antibiotic therapy, cephalothin or vancomycin and an associated aminoglycoside until the results of culture are available.3 A role for teicoplanin in the treatment of Gram-positive peritonitis has been suggested4 and the efficacy and safety of this antibiotic have been demonstrated in two prospective trials.5,6

Patients and methods

Seventy-three CAPD patients with peritonitis were enrolled from the six participating centres. Each patient underwent four daily exchanges with 2 litre bags using a Y-set with disinfectant. The study protocol was approved by the Ethical Committee of the University Hospital in Verona.

The diagnosis of peritonitis was based on the simultaneous presence of two of the following findings: abdominal pain, dialysate white cell count exceeding 100/mm3 and positive dialysate culture. Informed consent was obtained from each patient before the enrolment. Exclusion criteria were: known or suspected sensitivity to the study drug(s), peritonitis caused by tunnel infection, or effective antibiotic therapy in the previous 48 h.

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Patients were randomized prospectively to receive either teicoplanin plus tobramycin or cephalothin plus tobramycin. Blood and dialysate specimens were taken for haematological, biochemical and microbiological investigations, including WBC count, at several times during the study period, as shown in Table I.

Peritoneal dialysis fluid was obtained aseptically and cultured by inoculation into enrichment media. The isolated bacteria were identified and their susceptibility was determined by conventional laboratory methods.

Patients were instructed to inject the antibiotics into the bags and were allowed to go home, being hospitalized only if clinically indicated. The antibiotic schedules were as follows: Group 1: loading dose of teicoplanin 400 mg iv plus tobramycin 120 mg im, followed by administration via dialysis bag of teicoplanin 40 mg plus tobramycin 10 mg into each bag. Group 2: loading dose of cephalothin 2 g iv plus tobramycin 120 mg im, followed by administration of cephalothin 500 mg plus tobramycin 10 mg into each bag.

In both groups, antibiotics were injected into each bag in the first week of treatment, in alternate bags in the second week and in an overnight bag in the third week. Both groups were treated for a minimum of 15 days, and for at least 5 days after clearing of the dialysate (dialysate blood cell count less than 100/mm$^3$) and disappearance of the organism.

After identification of microorganisms and sensitivities, therapy was modified accordingly. (a) Group 1: (i) where a Gram-positive organism sensitive to teicoplanin was found, tobramycin was discontinued; (ii) where a Gram-negative organism was found, teicoplanin was discontinued; (iii) where there was no growth, teicoplanin and tobramycin were continued. (b) Group 2: (i) where a cephalothin-sensitive Gram-positive organism was found, tobramycin was discontinued; (ii) where a cephalothin-resistant and teicoplanin-sensitive Gram-positive organism was found, both tobramycin and cephalothin were discontinued and teicoplanin was started (only five patients followed this latter regimen, in order to avoid inappropriate therapy in the case of infection caused by methicillin-resistant staphylococci; thereafter, these five patients were excluded from the study). (iii) Where a cephalothin-sensitive Gram-negative organism was found, tobramycin was discontinued; (iv) where a cephalothin-resistant Gram-negative organism was found, cephalothin was discontinued; (v) where there was no growth, cephalothin and tobramycin were both continued.

Clinical outcome was evaluated as follows: ‘cure’: disappearance of all signs and symptoms related to infection and a decrease in white cells in the dialysate to less than 100/mm$^3$ for 4 weeks after therapy. ‘Failure’: no clinical improvement, or modification of therapy due to clinical deterioration, or removal of catheter.

Microbiological outcome was evaluated as follows: ‘Elimination’: disappearance of microorganism in dialysate during and for 4 weeks after the end of therapy. ‘Persistence’: persistence of microorganism in dialysate during or within 1 week from the end of the therapy. ‘Relapse’: a return of peritonitis with the same organism within 4 weeks after the end of the therapy.

Seventy-three patients were enrolled in the study, 39 in Group 1 and 34 in Group 2. In Group 2, five patients with methicillin-resistant Gram-positive bacteria were excluded from the study. The study protocol was completed in 68 patients: 39 patients in Group 1 (23 males and 16 females, age 66.7 ± 12 years) and 29 patients in Group 2 (13 males and 16 females, age 66.9 ± 13 years). The bacteria isolated in these patients are reported in Table II: 49 (84%) were Gram-positive, with no significant difference between the two groups. Three patients (two in Group 1 and one in Group 2) were excluded from the efficacy analysis based on clinical examination for methodological reasons. Twenty-three patients were excluded from the efficacy analysis based on bacteriological results (13 in Group 1 and 10 in Group 2) either because the pre-treatment culture results were negative (10 patients) or because the protocol time-schedule of bacteriological cultures was not followed (13 patients).

Statistical analysis was carried out using Fisher’s exact test and/or chi-square test as appropriate. Null hypotheses were rejected at $P < 0.05$.

**Results**

**Clinical evaluation**

A total of the 37 clinically evaluable patients (94.6%) in Group 1 (teicoplanin plus tobramycin) were

<table>
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<tr>
<th>Investigation</th>
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<th>day 3</th>
<th>Treatment</th>
<th>day 5</th>
<th>week 1</th>
<th>week 2</th>
<th>Post-treatment</th>
<th>week 1</th>
<th>week 4</th>
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Table I. Investigations
Teicoplanin and peritonitis in CAPD patients

cured, compared with 21 of 28 clinically evaluable patients (75%) in Group 2 (cepha lothin plus tobramycin) (P < 0.05). The incidence of failure was 4.6 times higher in Group 2 (25%) than in Group 1 (5.4%).

Microbiological evaluation

Elimination of pathogens was obtained in 23 of 26 bacteriologically evaluable patients (88.5%) in Group 1, in comparison with 14 of 19 bacteriologically evaluable patients (73.7%) in Group 2: this difference was not statistically significant. The infection persisted in four patients (21%) in Group 2 and in two patients (7.7%) in Group 1. Relapse was registered in one patient in Group 2 (5.3%) and in one patient in Group 1 (3.8%).

Safety

Local and systemic tolerability were good for both regimens. Transitory prurigo and erythema were reported by one patient treated with teicoplanin.

Discussion

Peritonitis is still a common clinical problem in patients on peritoneal dialysis, and many different antibiotic regimens have been suggested as treatments. A combination of vancomycin and an aminoglycoside has been recommended as a ‘first-line’ therapy because of the emergence of multi-resistant strains of coagulase-negative staphylococci. Good results have been reported with this combination therapy, giving primary cure rates of about 80%. However, the intraperitoneal use of vancomycin may be associated with chemical peritonitis, and vancomycin is potentially harmful to residual renal function, whose loss might require daily extraperitoneal dialysis exchange.

Recently, teicoplanin has been suggested as an alternative antibiotic to vancomycin: it is a glycopeptide antibiotic with a similar mode of action and spectrum to vancomycin (namely, activity against Gram-positive organisms), but with little or no ototoxicity or nephrotoxicity. In 1988, a pilot study showed teicoplanin to be an effective agent for the treatment of CA PD peritonitis. Only two additional studies have been performed: teicoplanin versus vancomycin and teicoplanin versus cefuroxime: the cure rates in patients treated with teicoplanin were 75 and 89% respectively, and did not differ significantly from controls. In contrast, in our study 94.6% of the peritonitis episodes treated with teicoplanin achieved complete resolution as compared with 75% of the cases treated with cephalothin (P < 0.05); the incidence of failure was 4.6 times higher in the cephalothin group than in the teicoplanin group. However, the two populations were comparable with regard to clinical and microbiological factors. Gram-positive bacteria were responsible for about 80% of peritonitis in both groups, and therefore the results obtained were the true consequence of the efficacy of teicoplanin.

We used the therapeutic regimen proposed by Neville et al., namely a ‘three-stage reducing-dose regimen’: this schedule was followed by excellent local and systemic tolerability and, at the same time, by an elevated, satisfactory, success rate.

The recent report by Klaus et al., stating that intermittent treatment schedules with teicoplanin are as effective as continuous administration, has to be confirmed by further studies. If other studies achieve the same results, a reduction of the cost of treatment for each therapeutic cycle could be obtained with the intermittent schedule.

This multicentre, comparative, randomized study confirms that the combination of teicoplanin plus tobramycin in the treatment of CAPD peritonitis is both highly effective and well-tolerated. This antibiotic association is more effective than cephalothin plus tobramycin and may become a ‘first-line’ treatment in the management of CAPD peritonitis.

<table>
<thead>
<tr>
<th>Microorganism</th>
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<th>Group 2</th>
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<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>16</td>
<td>12</td>
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<tr>
<td>Staphylococcus aureus</td>
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<td>7</td>
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<td>Streptococcus spp.</td>
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<td>Pseudomonas spp.</td>
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<td>Proteus spp.</td>
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<td>1</td>
</tr>
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<td>Klebsiella spp.</td>
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<td>1</td>
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<td>Others</td>
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References


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