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Intermittent Administration of Betalactam-Antibiotics for Treatment of Severe Infection in Hemodialysis Patients*

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Abstract: Infections are a leading cause of morbidity and mortality in hemodialysis patients. Still, due to altered pharmacokinetics and potential toxic sideeffects, safe and efficient antibiotic therapy in dialysis patients remains a major challenge. We reviewed our experience with intermittent administration of betalactam antibiotics for treatment of severe infections in hemodialysis patients.

A total of 81 episodes of infection in 45 patients was assessed. All patients were treated with betalactam antibiotics (cefepime in 11 episodes, cefpirom in 33 episodes, piperacillin in 9 episodes, amoxicillin in 18 episodes, ceftazidime in 10 episodes, respectively). All antibiotics were given post hemodialysis 3x per week. Treatment was considered efficient in case of a significant decrease in CRP in addition to clinical response.

Overall treatment success rate was 85% (69 episodes of infection). The decrease of CRP was 52% (6.9 ± 5.8 to 3.3 ± 4.9 mg/dl; p = 0.00003). The mean duration of treatment was 19 ± 13 days. Treatment was generally well tolerated.

We conclude, that severe infections in hemodialysis patients can be treated safely and efficiently with an empiric therapy with betalactam antibiotics. Intermittent administration, potentially allowing ambulatory treatment, is possible.

Key words: hemodialysis; infection; betalactams; intermittent administration; nephropharmacology

Introduction

Infections are a leading cause of morbidity and mortality in hemodialysis patients [1, 2]. Indeed, hemodialysis patients are inherently prone to infection as a result of compromised immune system caused by biochemical abnormalities or use of immunosuppressive agents [3, 4, 5]. Moreover, malnutrition and advanced age may further impair the immune system as may comorbid conditions such as diabetes or underlying systemic disease [6, 7, 8, 9, 10].

Bacteremia in hemodialysis patients is primarily due to access site infection including access manipulation and hemodialysis procedure. Infection is most common with central-vein catheter access, followed by arteriovenous grafts; infection of the standard arteriovenous fistula is rare [4, 9, 11, 12].

Other types of infection include pneumonia/bronchitis, skin and soft tissue infections and infections of the genital and urinary tract, accounting for up to 50% of bacteremia in hemodialysis patients [3].

Grampositive cocci are the main cause of bacteremia in hemodialyis patients, accounting for up to 50% of isolated organisms. Staphylococcus aureus, coagulase-negative staphylococcus, pseudomonas aeruginosa, escherichia coli, klebsiella species and enterobacter species are the most frequent pathogens isolated in hemodialysis patients [3]. Therefore, early empiric antimicrobial therapy should also include coverage for gramnegative organisms [4].

We sought to determine the tolerability and efficacy of intermittent administration of betalactam antibiotics for therapy of infection in chronic hemodialysis patients.

Material and Methods

We report our experience with intermittent administration of betalactam-antibiotics for treatment of severe infections in hemodialysis patients. The dose of antimicrobial drugs was based on the interdialytic half-lifes assumed for hemodialysis patients: Cefazolin ($t_{1/2}$ = 34.7 ± 5.9 h) [13], cefepime ($t_{1/2}$ = 22.0 ± 2.14 h) [14], cefpirom ($t_{1/2}$ = 9.35 ± 0.99 h) [15]. The dosages of piperacillin/tazobactam, amoxicillin/clavulanicacid and ceftazidime were calculated from the dosage recommendations of the above mentioned cephalosporins. The half-lifes of teicoplanin were $t_{1/2\alpha}$ 0.37 ± 0.25 h, $t_{1/2\beta}$ 20.1 ± 7.1 h and $t_{1/2\gamma}$ 549.7 ± 210.5 h as published previously [16]. The vancomycin half-life (anuric patients 150 h) was derived from a previously published review about antimicrobial drugs and renal replacement therapy [17].

Patients

We reviewed the medical records of patients undergoing chronic hemodialysis and presenting with clinical signs and symptoms of infection. Complete medical charts, including documentation of signs and symptoms and routine laboratory tests of patients undergoing chronic hemodialysis at the Department of Internal Medicine III, Divison of Nephrology and Dialysis,

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between December 1st, 1997 and April 30th, 2003 were analysed.

All patients treated with betalactam-monotherapy were evaluated. For subgroup analysis, patients treated with combination therapy betalactam plus glycopeptide and patients treated with glycopeptide-monotherapy were evaluated separately.

Infection

Diagnosis of infection included a significant elevation of C-reactive protein (CRP) in addition to standard criteria [3]. Treatment of infection was defined as therapy with a betalactam-agent, administered post hemodialysis 3 times a week. Treatment was continued for a period of at least six days (at least three doses) in all patients.

Microbiology

Microbiological analysis was performed in all patients. Blood cultures were collected in addition to specimens obtained from the site of infection, compatible with the clinical diagnosis. All isolates recovered from cultures of blood were recorded, specimens from central catheters were recorded if > 15 colonies were present; all isolates from normally sterile fluids were included [3, 18, 19]. All cultures were performed before or within 24 hours after initiation of antimicrobial treatment.

Treatment and Treatment Response

All betalactam- and glycopeptide-antibiotics were diluted in physiologic saline and administered intravenously after the end of the dialysis session, three times a week. Treatment response was assessed by monitoring of CRP, white blood cell count (WBC) and assessment of clinical signs and symptoms. Treatment efficacy was defined as a significant decrease in CRP [20, 21], successful treatment of any baseline bacterial infection, absence of any breakthrough infection during therapy. Treatment duration, as defined as total days of antimicrobial therapy, was recorded.

Side Effects

All adverse events possibly related to the antimicrobial therapy were recorded.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation. Groups were compared using the two-tailed Student *t* test for continuous variables. A p-value of less than 0.05 was considered statistically significant.

Results

Patients

During the study period, a total of 81 episodes of infection was treated in 45 patients. Twentythree men and 22 women (age 60.5 ± 13.3 years, weight 66.1 ± 14.4 kg) were included. All patients underwent chronic hemodialysis three times a week. Mean duration of dialysis was 4.2 ± 0.2 h.

Clinical Infections

Dialysis related infections (including infections of the arteriovenous graft and infections of the central venous access) accounted for 6 cases, other infections identified included respiratory tract infections (7 cases), urinary tract infections (5 cases) and wound-infections (5 cases). In most cases (n = 58), no obvious cause of infection could be identified.

Microbiological Findings

In 28 episodes of infection 41 organisms were isolated. A total of 19 grampositive cocci and 16 gramnegative rods were identified. Isolates most frequently cultured were *staphylococcus epidermidis* (8 cases), *staphylococcus aureus* and *coagulase negative staphylococcus* (7 cases), and *pseudomonas* species (8 cases). Other specimens isolated comprised *enterococcus* species (3 cases), *peptostreptococcus* (1 case), *enterobacteriaceae* (3 cases), *e.coli* (2 cases), *proteus* (1 case), other gramnegative rods (2 cases), *corynebacteriae* (3 cases), *lactobacillus* (1 case), *bacteroides* (1 case) and *candida sp.* (1 case).

Antimicrobial Therapy

Empirical antimicrobial therapy with betalactam antibiotics was initiated in all patients. Most patients were treated with third-generation cephalosporin antibiotics: Thirtythree patients received cefpirom (2g) and 11 patients received cefepime (2g). Ceftazidime (2g) was given in 10 patients. Piperacillin/tazobactam (4g) was given in 9 patients. Eighteen patients received therapy with amoxicillin/clavulanacid (2.2g).

Patients receiving a combination therapy of betalactam and glycopeptide and patients receiving glycopeptide monotherapy were evaluated separately. A combination therapy of betalactam and vancomycin was initiated in 14 episodes of infection in 8 patients. Seven patients (13 episodes of infection) were treated with vancomycin 500mg post dialysis and cefpirom, 1 patient was treated with vancomycin and ceftazidime. Six patients, presenting with 9 epsiodes of infection, were treated with a monotherapy of teicoplanin 400 mg post dialysis.

Response to Treatment

In the analysis of response, 81 episodes of infection in 45 hemodialysis patients receiving betalactam-monotherapy were entered. Overall success rate was 85% (69 episodes of infection). Decrease of CRP during treatment was 52% (6.9 ± 5.8 to 3.3 ± 4.9 mg/dl; p = 0.00003); WBC was somewhat lower at the end of the treatment (7.4 ± 2.7 to 7.3 ± 3.8 G/l). The mean duration of antimicrobial treatment was 19.2 ± 12.8 days.

Subgroup Analysis

Subgroup analysis of patients receiving betalactam monotherapy showed a favourable response (defined

as a significant decrease in CRP) for patients treated with cepirom, cefepime and amoxicillin/clavulanacid.

For patients treated with cefpirom (n = 33), success rate was 91%. The decrease of CRP during treatment was 67% (7.3 ± 6.3 to 2.4 ± 3.0 mg/dl; p = 0.0003); WBC decrease was slight (7.1 ± 2.2 to 6.5 ± 1.9 G/l). Duration of therapy was 20.4 ± 12.5 days.

For patients treated with cefepime (n=11), success rate was 82%. The decrease of CRP was 64% (9.4 ± 5.4 to 3.4 ± 3.3 mg/dl; p = 0.02); WBC decrease was slight (7.8 ± 1.8 to 6.5 ± 2.2 G/l). Duration of therapy was 26.2 ± 15.7 days.

For patients treated with amoxicillin/clavulanacid (n = 18), success rate was 100%. The decrease of CRP during treatment was 45% (4.0 ± 5.6 to 2.2 ± 4.0 mg/dl; p = 0.009); however, a slight increase in WBC was observed (6.6 ± 1.3 to 7.2 ± 1.8 G/l). Duration of treatment was 12.8 ± 6.1 days.

63% of patients treated with ceftazidime (n=10) showed no decrease of CRP (7.6 ± 4.8 to 7.3 ± 10.4 mg/dl; n.s.), an increase of CRP was observed in 37% (7.6 ± 4.8 to 11.6 ± 9 mg/dl; n.s.). WBC decreased slightly (11.0 ± 5.7 to 10.9 ± 7.7 G/l). Duration of treatment was 21.6 ± 10.1 days.

67% of patients treated with piperacillin/tazobactam (n=9) showed a decrease of CRP (8.1 ± 7.0 to 3.6 ± 4.7 mg/dl; n.s.), an increase of CRP was oberved in 33% (8.1 ± 7.0 to 5.6 ± 4.8 mg/dl; n.s.). WBC decreased slightly (9.5 ± 6.2 to 9.0 ± 2.3 G/l; n.s.). Duration of treatment was 24.4 ± 19.4 days.

For patients treated with cefpirom and vancomycin (n=13) or ceftazidime and vancomycin (n = 1), success rate was 86%. The decrease of CRP during treatment was 69% (13.5 ± 11.1 to 4.1 ± 4.1 mg/dl; p=0.01); however, a slight increase in WBC was observed (7.1 ± 2.4 to 8.0 ± 2.1 G/l). Duration of treatment was 22.8 ±11.4 days.

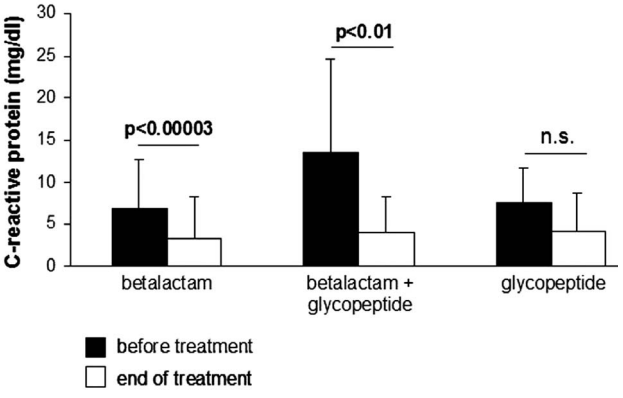

Fig. 1. Course of C-reactive protein in hemodialysis patients under various antibiotic regimens.

For patients treated with teicoplanin monotherapy (n = 9), success rate was 66%. The decrease of CRP during treatment was 44% (7.6 ± 4.1 to 4.2 ± 4.6 mg/dl; n.s.), WBC decrease was clinically irrelevant (5.6 ± 2.5 to 5.5 ± 1.8 G/l). Duration of treatment was 25.6 ± 8.3 days (Fig. 1).

Safety Analysis

There were three adverse events possibly associated with betalactam therapy: exanthema in two patients (one patient receiving cepirom, one patient receiving cefepime) and mental confusion in one patient (receiving cefepime). However, no discontinuation of therapy was necessary. In four patients, break-through infections with Candida spp. were documented, all of which could be successfully treated with fluconazole therapy.

Discussion

In the present study we retrospectively assessed the clinical efficacy of empirical therapy with betalactam antibiotics for treatment of severe infections in hemodialysis patients. In our study all patients received intermittent administration of betalactams.

Therapy of infections in hemodialysis patients has ever been a major problem and growing resistance and the emerge of new and multiresistant pathogens are a new challenge.

A number of studies proposed early therapy with glycopeptide antibiotics in patients undergoing chronic hemodialysis and presenting with clinical signs of infections [22]. Glycopeptide antibiotics were favoured due to their excellent activity against grampositive pathogens including MSSA and MRSA. However, increased use has led to growing resistance [23, 24]. Moreover, glycopeptide use is often limited due to toxic side effects.

In contrast, recent evidence suggested early and empirical therapy to cover both grampositive and gramnegative pathogens. In this context, the use of broad spectrum betalactam antibiotics has been widely recommended [25, 26].

Third generation cephalosporin antibiotics show good in vivo and in vitro activity against common grampositive bacteria including staphylococci and streptococci, the specimens most frequently isolated in hemodialysis patients. Moreover, they show excellent activity against gramnegative bacteria including pseudomonas species, bacteria associated with considerable mortality.

Recently published trials have eluciated a favourable pharmacokinetic profile for cefpirom and cefepime. It has been shown that intermittent administration of a standard dose of 2g following dialysis led to serum concentrations 4x MIC for most target pathogens and serum concentrations exceeded MIC for the entire dosing interval, thus allowing maximum antibacterial killing [14, 15, 27, 28, 29].

Based on these data, we reviewed our clinical experience with intermittent administration of betalactam antibiotics for treatment of severe infection in hemodialysis. Treatment response was favourable in 91% of patients treated with cefpirom and in 82% of patients treated with cefepime. These rates were comparable to success rates achieved by a combination therapy of cephalosporin/vancomycin (86%). Treatment response was lower for therapy with ceftazidime, because of the almost no activity against grampositive pathogens.

In case of suspected or proven community acquired pneumonia or respiratory tract infections, frequently

therapy with amoxicillin/clavulanacid was initiated. Treatment success was especially high in this patient group (100%).

In contrast, a monotherapy with teicoplanin resulted in a markedly lower response rate of only 66%. Teicoplanin therapy was initiated in case of suspected grampositive organisms, in most cases infections of the central venous access were suspected. The worse treatment response clearly shows that a glycopeptide antibiotic is justified only in infections of central venous access. We hypothesize that catheter associated infections can only be cured if the foreign body is removed (data not evaluated), and in hemodialysis patients with diabetic foot syndrome a pure grampositive antimicrobial therapy is not adequate. In fact, the specimens isolated showed a high rate of infections with gramnegative bacteria, therefore, treatment failure for teicoplanin monotherapy is explained.

Considerable debate has focused on the administration of betalactam antibiotics. It is generally accepted that continuous administration might lead to a somewhat favourable response based on the so-called ´time-dependent´ pharmacodynamics in some cases [30, 31]. However, it is known that pharmacokinetics are significantly altered in case of renal failure [32]. A significant prolongation in half-life can be observed. Consequently, a dose reduction or interval prolongation is mandatory in patients with various degrees of renal insufficiency. Patients undergoing chronic hemodialysis pose a special challenge. Optimal antimicrobial therapy is necessary for sufficient treatment of infection. To ensure maximum antibacterial activity, in patients treated with betalactam therapy, serum concentrations have to exceed the MIC of the target pathogens for the entire dosing interval, best antibacterial activity is given at a serum concentration exceeding the MIC 4 times. It has been demonstrated recently that intermittent administration of betalactams, when given post hemodialysis, leads to serum concentrations fulfilling these criteria [14, 15]. Based on these data, in our institution most patients treated with betalactams for severe infection received intermittent antibiotic administration. Indeed, in the present study we show - based on pharmacokinetic data previously published - a favourable clinical response for the majority of infectious episodes. Severe adverse drug events were not recorded and no increased rate of infections with candida species was seen although most patients received a broad-spectrum antimicrobial therapy almost three weeks.

In conclusion, we show that severe infections in hemodialysis patients can be treated efficiently with betalactam bolus therapy. In our study, clinical response rates for broad-spectrum betalactam monotherapy were high, comparable to response rates achieved by a combination therapy betalactam and glycopeptide. Intermittent dosing (administration post hemodialysis/ three times a week) was performed and was well tolerated.

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