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Ceftriaxone Is an Efficient Component of Antimicrobial Regimens in the Prevention and Initial Management of Infections in End-Stage Renal Disease

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Key Words

End-stage renal disease · Ceftriaxone · Hemodialysis · Peritoneal dialysis · Renal transplantation · Infections

Abstract

Background: Infection is a frequent complication in patients with end-stage renal disease. The most common organisms isolated are gram-positive cocci and gram-negative bacilli. Therefore, the usual initial therapeutic approach in these situations is the simultaneous intravenous administration of vancomycin plus an aminoglycoside. This treatment's adverse effects include ototoxicity, nephrotoxicity, and less than ideal tissue penetrance. ***Methods:*** We assessed the efficacy of intravenous ceftriaxone in the prevention and in the initial empirical treatment of infections in end-stage renal disease patients, and tested the stability of blood levels of this antibiotic in this population. We studied 104 patients, 65 of them falling into the prevention group (1 g of ceftriaxone i.v. for 5 days) and 39 into the treatment group (1 g of ceftriaxone i.v. or intraperitoneally for 10–14 days). ***Results:*** Peak serum ceftriaxone concentrations were well above the minimal inhibitory concentration for 90% of strains. Trough serum concentrations of the drug prior to the next dose were also considerably in excess of the minimal inhibitory concentration. In the prevention group, 8 of 65 developed an infection, which was sensitive to ceftriaxone, whereas in 22 of the 39 patients from the treatment group, cultures showed organisms sensitive to ceftriaxone and in the remaining 17 patients sensitivity was not done. ***Conclusions:*** The present study demonstrates the efficacy of a simplified dosing schedule in achieving blood levels of the antibiotic well in excess of minimal inhibitory concentration of any of the organisms encountered. It also shows the usefulness of ceftriaxone in the prevention and/or treatment of bacterial infections and the lack of the side effects vancomycin and/or aminoglycosides possess.

Patients with end-stage renal disease (ESRD) undergoing chronic maintenance hemo- or peritoneal dialysis are extremely prone to the development of infections [1–3]. The frequency of infections in this population is in part due to the immunosuppressive effects of uremia [1, 4–9], but a significant added factor is the frequent violation of the integrity of the vascular system with each hemodialysis session [1], or of the peritoneal cavity with the daily exchange of peritoneal dialysis fluid and the manipulation of the peritoneal catheter [3, 10–12]. The most frequent

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organisms encountered in ESRD patients are *Staphylococcus* species, *Streptococcus* species, *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* [1, 10–12]. Heretofore, the most common initial approach to the treatment of infections in ESRD patients has been the concurrent use of an intravenous loading dose of vancomycin and of an aminoglycoside followed by the respective maintenance dose of each drug. The shortcomings of this treatment include ototoxicity and an incidence of 20% of nephrotoxicity with aminoglycosides (the frequency of renal parenchymal damage rises as therapy is prolonged, reaching 50% with 14 days or more of therapy [13]), and a 5% incidence of nephrotoxicity with vancomycin [14].

Ceftriaxone is a third generation parenterally administered cephalosporin with a broad spectrum of activity against most aerobic gram-positive and gram-negative bacteria and a few anaerobic organisms. It has a very low toxicity profile, the longest elimination half-life and protein binding that is highest among third-generation cephalosporins, and is saturable [15, 16]. In addition, ceftriaxone offers the advantages of once daily dosing, minimal drug clearance during dialysis, and established efficacy [15–20]. These advantages may translate into cost-effectiveness.

The following study was conducted to determine the utility of ceftriaxone in ESRD and its efficacy in treating or preventing infections, and to assess the stability of trough and peak levels of this drug in this population.

Materials and Methods

Patient Characteristics

One hundred and four (104) patients (63 men and 41 women) with ESRD were included in the study. All patients were undergoing either hemodialysis (n = 46), peritoneal dialysis (n = 29), or were kidney transplant recipients (n = 29). Signed informed consent was obtained from all subjects. The mean age of the subjects was 41.8 (range 22–74) years. Patients were divided into two groups: (1) Prevention group (n = 65), which included 16 patients receiving preventive treatment in conjunction with the placement of a peritoneal dialysis catheter, 20 hemodialysis patients admitted for the placement or revision of an arteriovenous fistula or graft, and 29 renal transplant recipients (serum creatinine 1.9 ± 0.5 mg/dl). In this group, 27 patients received ceftriaxone alone, 9 patients received ceftriaxone plus other antibiotics, and the 29 renal transplant recipients received in addition cotrimoxazole for *Pneumocystis carinii* prophylaxis. (2) Treatment group (n = 39), which included 13 patients undergoing peritoneal dialysis and 26 patients undergoing hemodialysis. These patients received ceftriaxone as initial treatment for signs and symptoms of peritonitis (intraperitoneal instillation, i.p.), bacteremia, pneumonia, or other systemic infections. In this group, 11 patients received ceftriaxone as the only antibiotic, and the remaining 28 received ceftriaxone plus other antibiotics. With respect to hemodialysis, at the time the study was performed, CA 110 (Baxter) hollow fiber-cellulose acetate dialyzers were used.

Drug Administration and Sample Collection

Every patient falling into one of the above-mentioned groups had a complete blood count, and sputum, blood, urine and/or peritoneal fluid cultures in appropriate. Each hemodialysis patient or renal transplant recipient then received 1–2 g of intravenous ceftriaxone over 3–5 min; this dose was repeated every 24–48 h. Patients in the prevention group received ceftriaxone 1 g i.v. for 5 consecutive days starting 48 h prior to the surgical procedure. For patients with peritonitis the dose used was 1 g i.p. as a loading dose and 125 mg/l of dialysate for 4 doses (exchanges) for 10–14 days. For patients undergoing hemodialysis 3 times a week the dose of ceftriaxone given was 1 g intravenously after each dialysis session, except following the last dialysis treatment of the week, when the dose was increased to 2 g (because of the longer interval until the following dialysis).

In cases where an actual infection was being treated that did not appear to be responding satisfactorily to the drug, or where the suspected infecting organisms were not uniformly susceptible to the drug, the antibiotic regimen was adjusted either by the addition or by the substitution of a more appropriate antibiotic treatment.

Blood Samples

Blood samples were drawn 30 min after an intravenous dose of 1 h after an i.p. dose for measurement of peak serum drug level (P_1), and immediately prior to dialysis and/or the next dose for measurement of trough serum drug level (T_1). These measurements were repeated on day 5 of ceftriaxone administration (P_2 and T_2, respectively). Blood samples were centrifuged within 4–6 h to separate the plasma. Plasma samples were kept frozen at –20 °C until analysed. Ceftriaxone serum concentrations were measured using high-performance liquid chromatography.

Results

Peak and trough serum values for ceftriaxone in plasma in all patients enrolled in the study are depicted in figures 1 and 2, respectively. In each figure, the range of the minimal inhibitory concentration for 90% of strains (MIC_{90}) for most organisms encountered in ESRD patients is indicated. It can be seen from figure 1 that peak serum ceftriaxone concentrations were well above the MIC_{90} in every instance. Figure 2 shows that trough serum ceftriaxone concentrations present prior to the second dose were also considerably in excess of the MIC_{90}. In the 46 patients undergoing hemodialysis the ceftriaxone dosing was given after each dialysis treatment only. Thus, trough serum levels in these patients represent persistence of the antibiotic in useful concentrations for as long as 2–3 days. There was no tendency for ceftriaxone to accumulate with repeated use. P_1 (135 ± 58 μg/ml) and P_2 (140 ± 56 μg/ml) values did not differ significantly, nor did T_1

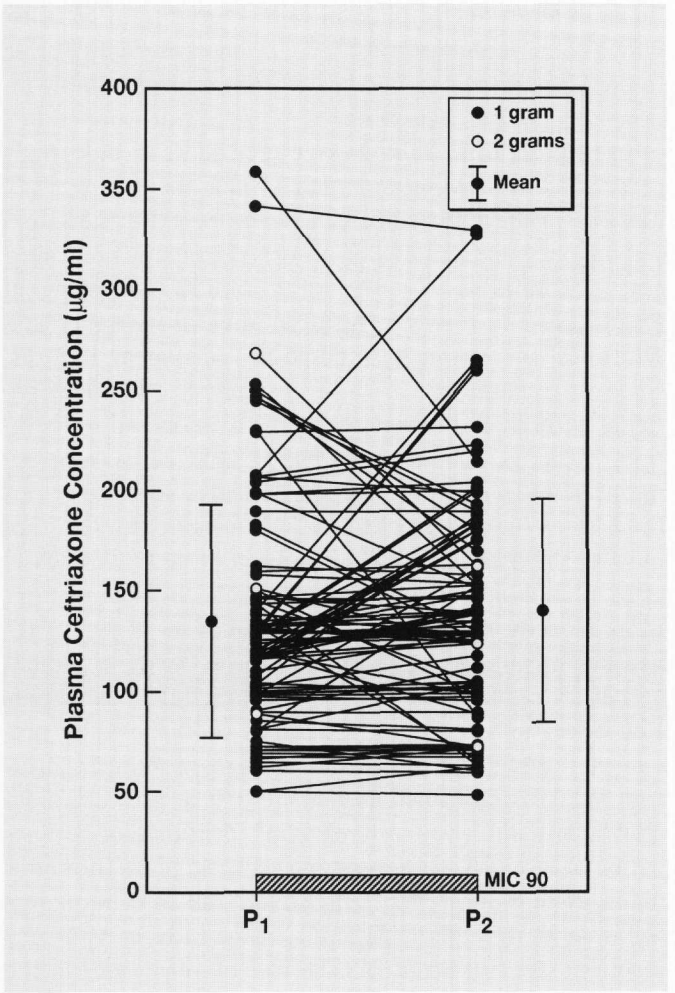

Fig. 1. Initial (P_1) and final (P_2) plasma ceftriaxone peak levels.

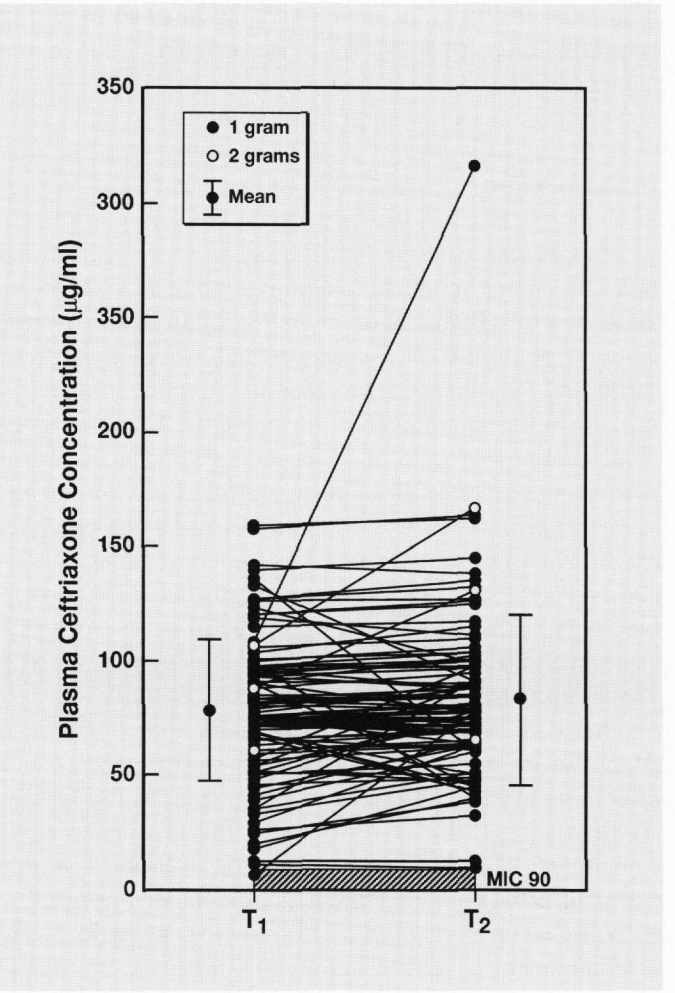

Fig. 2. Initial (T_1) and final (T_2) plasma ceftriaxone trough levels.

(78 ± 31 μg/ml) and T_2 values (83 ± 37 μg/ml) (fig. 1, 2). Peak serum levels always exceeded the MIC_{90} of the organisms encountered, and trough serum levels exceeded the MIC_{90} in all but 6 instances, so that 96% of all levels (P+T) were above the MIC_{90}.

Sixty-six patients (63.5%) received other antibiotics besides ceftriaxone: All 29 transplant recipients received cotrimoxazole for *P. carinii* prophylaxis. Thirty-seven patients (9 from the prevention group and 28 from the treatment group) received either vancomycin, clindamicin, tobramycin or ciprofloxacin. Of the 38 patients (36.5%) who received only ceftriaxone, 27 were for prevention and 11 for treatment. Among the 65 patients from the prevention group, 8 of them developed an infection that was sensitive and resolved with ceftriaxone. In the 39 patients from the treatment group, 22 cultures showed organism(s) sensitive to ceftriaxone and in the remaining 17 sensitivity was not done. In this group, all patients received ceftriaxone, but in 28 patients other antibiotics had to be added.

The most frequent organisms encountered in our patients were basically the same as previously reported by other authors [1, 10, 12]: *Staphylococcus* species with MIC_{90} of 0.02–0.08 μg/ml; *Streptococcus* species with MIC_{90} of 0.001 to 0.002 μg/ml; *Escherichia coli* with MIC_{90} of 0.06–0.4 μg/ml, *Klebsiella* with MIC_{90} of 0.1 to 1.0 μg/ml and *P. aeruginosa* with MIC_{90} of 0.03–0.06 μg/ml. These MIC_{90} values contrast with the much higher drug levels attained with the dosing schedule employed in the present study (fig. 1, 2). The most common adverse effects reported with ceftriaxone, such as hypersensitivity reactions, diarrhea, thrombocytopenia, throm-

bocytosis, eosinophilia, leukopenia, abdominal pain, and hepatotoxicity [15, 16] were not encountered in the present study.

Discussion

The present study shows the efficacy of a simplified and safe dosing schedule in achieving blood levels of the antibiotic well in excess of the MIC_{90} of any of the organisms encountered. It also shows that whether alone or combined, ceftriaxone is an efficient component of an initial antibiotic approach for the prevention and/or treatment of known bacterial infections in the majority of patients regardless of the administration route. Moreover, as the nephrotoxicity of cephalosporins is considerably lower compared to that caused by vancomycin or aminoglycosides [13, 14, 21], it does not impair renal function in kidney allograft recipients, and the residual creatinine clearance in dialysis patients is better preserved, thereby contributing to the better management of uremia.

There are several reasons why ceftriaxone is a useful, practical, and safe therapeutic tool in the management of infections in ESRD patients. Ceftriaxone has the longest elimination half-life ($T_{1/2}$) of any of the third-generation cephalosporin antibiotics, ranging from 6 to 8.5 h in normal subjects [15–17], which does not change appreciably with age except in neonates (18.6 h) [15]. Its major route of elimination is via the kidney (41–60%), wherein it is disposed by glomerular filtration without any significant renal tubular secretion [15, 16, 22]; the remainder is excreted in the bile [15, 16]. In ESRD patients the $T_{1/2}$ of the drug has been reported to be much longer but variable, ranging from 11.7 to 17.3 h [19, 23, 24]. It has been shown that ceftriaxone is not removed to any significant extent from plasma by hemodialysis [19, 20]. Thus, in these patients ceftriaxone is a truly once-a-day antibiotic. Ceftriaxone is also the most protein-bound of the third generation cephalosporins (83–96%) [16]. However, the protein binding of ceftriaxone is saturable, such that at higher doses there is a lower percentage of ceftriaxone bound to protein. In this regard, it is considered therapeutically advantageous to give ceftriaxone in a large single dose because of the disproportionate increase in peak free concentration with increasing dose [25, 26]. Thus, after intravenous administration of 1–2 g of ceftriaxone, blood levels are in the order of 50–150 μg/ml, well above the MIC_{90} for most susceptible organisms, which ranges between 0.2–8 μg/ml [15, 16]. Also the tissue concentrations of the drug are maintained above the MIC_{90} for most pathogens for a 24-hour dosage interval [18]. In addition, ceftriaxone is bactericidal for most susceptible strains at or close to the MIC_{90} [16]. Studies with blisters and with skin windows, as well as sampling of a variety of body fluids including peritoneal fluid, have revealed concentrations of ceftriaxone severalfold higher than the MIC_{90} [27], demonstrating a superior tissue penetrance. Furthermore, ceftriaxone is extremely well absorbed from the peritoneal cavity, approximately 39% of it rapidly appearing in serum [28–30]; this is a feature of great importance and relevance for patients undergoing peritoneal dialysis, since ceftriaxone can be administered i.p. to these patients without the necessity for intravenous administration. Moreover, it has been shown that ceftriaxone remains stable when stored in peritoneal dialysis solutions for 24 h at room temperature [31]. Despite the fact that most cephalosporins exert an inhibitory, and even toxic, effect on human peritoneal mesothelial cells when administered locally, thereby delaying the recovery of the peritoneal surface and perhaps contributing to the development of peritoneal fibrosis, ceftriaxone lacks this dangerous side effect and can be given safely at the usually prescribed doses [32]. Cephalosporins rarely produce significant renal toxicity when used alone [17], a feature of great relevance if the residual creatinine clearance of dialysis patients were to be preserved, as it contribues to the better management of uremia. Moreover, the antibiotic was well-tolerated by all the patients in this study, and adverse reactions did not occur. As the role of antibiotics in the prevention of infections associated with the placement of a peritoneal dialysis catheter [33–35] or the placement or revision of an infected fistula or graft is not fully assessed in the literature, an empirical and seemingly long-acting antibiotic prophylactic regimen was employed in this prone-to-infections population. Finally, it is known that in patients on hemodialysis the clearance of ceftriaxone depends, among other factors, on the dialyzer membrane material used, on the surface area of the dialyzer, and on the albumin plasma concentration [36]. Nevertheless, our results show that therapeutic blood levels of the drug are readily achieved and well exceed the MIC_{90} in all the cases when the drug is given following dialysis, thereby eliminating any effect of dialysance of the drug. This simplified schedule offers a safe, practical, and efficient way to deal with infections in the vast majority of ESRD patients.

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