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Aztreonam can safely be used in combination with cyclosporin without aggravating nephrotoxicity

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Abstract. The administration of antibiotics to renal transplant patients using cyclosporin can be difficult because of the risk of severe nephrotoxicity. An investigation was therefore carried out to determine whether aztreonam, a synthetic monocyclic β-lactam antibiotic, can safely be combined with cyclosporin. In this retrospective study 68 renal transplant patients who received preoperative antibiotic prophylaxis consisting of aztreonam, ampicillin, and lincomycin were compared with 68 patients who received ceftazidime instead of aztreonam. Both groups were treated with cyclosporin and prednisolone and followed for 3 months. After transplantation 28.7% of the patients suffered from an acute renal failure and 1.5% had a wound infection. There were no significant differences between the two groups in acute renal failure, wound infections, other infections, incidence of rejections, duration of admission, or graft survival. We therefore conclude that aztreonam can safely be administered together with cyclosporin. We also conclude that the combination of aztreonam, ampicillin, and lincomycin is a good preoperative antibiotic prophylaxis in renal transplant patients.

Key words: Cyclosporin, interaction with aztreonam - Aztreonam, cyclosporin, nephrotoxicity.

There is now overwhelming evidence that cyclosporin improves graft survival in comparison with conventional immunosuppression with azathioprine [1, 5]. However, one of the major drawbacks of cyclosporin is its nephrotoxicity, particularly when administered together with other nephrotoxic drugs. Some antibiotics are especially hard to combine with cyclosporin [7, 9, 13, 15, 18, 19], and it may, therefore, be difficult to safely treat a severe infection in patients on cyclosporin. Recently, it has been shown that ceftazidime can safely be administered with cyclosporin [15, 18]. In the present study, we investigated whether aztreonam, a new synthetic monocyclic β-lactam antibiotic [2, 3, 11, 14], can be combined with cyclosporin without aggravating nephrotoxicity.

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Patients and methods

Included in this retrospective study were 136 renal transplant recipients, 68 of whom were treated with 2 g aztreonam IV, 1 g ampicillin IV, and 600 mg lincomycin IM as antibiotic prophylaxis before transplantation. These patients were compared with 68 consecutive patients who had received renal transplants in the period just prior to the study period and who had been treated with 2 g ceftazidime IV instead of aztreonam as part of the antibiotic prophylaxis. For both groups of patients, the antibiotic prophylaxis was given just before the start of the operation. Cyclosporin was started intravenously 6 h after revascularization of the graft in a dose of 3 mg/kg body weight for 3 days. Doses were not adjusted during the period of intravenous cyclosporin. Thereafter, cyclosporin treatment was continued orally in a dose of 15 mg/kg during the first 2 weeks. Two weeks after transplantation the dose was decreased by 4 mg/kg, and subsequently every 2 weeks by 2 mg/kg. These oral doses were adjusted according to the cyclosporin trough level or when nephrotoxicity was suspected. All patients also received 100 mg prednisolone for 3 days after transplantation and 10 mg daily thereafter. All patients were followed for 3 months.

Acute renal failure (ARF) was defined as a urinary production of less than 400 ml per 24 h. A wound infection was defined as an infection of the operation area that either had to be treated with antibiotics or required an operation.

Results

Sixty-eight of the 136 renal transplant patients included in this study received an antibiotic prophylaxis containing aztreonam and 68 received ceftazidime. Both groups were comparable in terms of

Table 1. Follow-up data of patients in the first 3 months after renal transplantation in relation to the prophylactic antibiotic given

	Prophylactic antibiotic		
	Aztreonam ($n=68$)	Ceftazidime ($n=68$)	
Patients with ARF (%)	29.4	27.9	NS
Postoperative hyperkalemia[a] (%)	20.6	23.5	NS
Mean number of urinary tract infections	1.4± 2.1	0.8± 1.4	NS
Mean number of respiratory tract infections	0.1± 0.3	0.1± 0.3	NS
Number of patients with a wound infection	2	0	NS
Percentage of patients without an acute rejection	58.8	66.2	NS
Mean number of admission days	22.8±13.6	24.0±17.9	NS
Mean number of readmissions	0.5± 0.7	0.6± 0.7	NS

[a] Hyperkalemia requiring immediate dialysis

sex, percentage of living related transplantations, match grade, and total ischemia time. A significantly higher recipient age and longer anastomosis time of the graft were found in the group receiving aztreonam. In the first 3 months after transplantation, 28.7% of the patients suffered from an ARF, 41.9% had one or more urinary tract infections, and 1.5% had wound infections. The incidence of ARF and postoperative infections in relation to the kind of prophylactic antibiotic given is shown in Table 1. No differences were found between the two groups. Two patients in the aztreonam group had a wound infection for which reoperation was necessary.

Discussion

From the literature it is known that several antibiotics and chemical agents, when combined with cyclosporin, result in an increased nephrotoxicity, among them aminoglycosides [15, 18, 19], amphotericine [15, 18], erythromycin [7, 9], and cotrimoxazole [7, 15, 18]. No adverse results have been reported on the combined use of cyclosporin with penicillin, ampicillin, furadantin, or lincomycin, and we have recently shown that ceftazidime can safely be used together with cyclosporin [15, 18]. Because cyclosporin is an immunosuppressive drug, infections frequently occur during its administration [8, 10, 12, 16, 17]. It is therefore essential that the number of antibiotics that can safely be administered with it be increased. Because aztreonam has an antibiotic spectrum that resembles that of aminoglycosides [2–4] and because it has a good safety profile without nephrotoxicity [3, 11, 14], it would theoretically be a good candidate for antibiotic treatment during cyclosporin therapy. Aztreonam has good activity against gram-negative organisms (with variable activity against *Pseudomonas aeruginosa*) but lacks significant effect against gram-positive and anaerobic organisms [2–4, 11, 14]. Aztreonam can be used in patients allergic to penicillin or cephalosporins [4]. The renal excretion of aztreonam is 60%–70% of the total drug excretion. It can be removed by dialysis and can safely be used in patients with diminished renal function ($t^1/_2$ 4.9–8.1 h). During longer therapy, when the creatinine clearance is less than 30 ml/min, dosage should be reduced to 50%. Adverse reactions are not very frequent and nephrotoxicity has not been described [11, 14]. There are no major interactions with cephradine, clindamycin, gentamicin, naficillin, or metronidazole [3].

In this study the same incidence of ARF was found in the group of patients who received aztreonam as in the patients treated with ceftazidime. Previously we found that gentamicin, used as a prophylactic antibiotic in the same way that aztreonam was used in this study, was severely nephrotoxic in combination with cyclosporin [15]. In addition, the number of patients needing immediate dialysis after transplantation because of hyperkalemia was similar in the two groups. Some differences, however, were found between the two groups. Age and anastomosis time were both higher in the group receiving aztreonam; thus, more ARF was expected in this group. No differences were found in the incidence of rejections, duration of admission, or graft survival. From various studies it is clear that the use of antibiotic prophylaxis in renal transplant patients decreases the frequency of both wound infections and mortality [6, 8, 10, 12, 16, 17, 20]. Several prophylactic combinations have been used with different, but mostly beneficial, effects. We previously showed that the combination of ceftazidime, lincomycin, and ampicillin was successful in preventing postoperative infections [15]. With aztreonam instead of ceftazidime, no differences were found in the incidence of wound infections or any other kind of infection. Compared with the 0.8%–11.3% incidences of wound infections with antibiotic prophylaxis reported in the literature, that found in our study was relatively low [6, 10, 12, 16, 17].

We conclude from this study that aztreonam can safely be administered with cyclosporin and that the combination of aztreonam, ampicillin, and lincomycin is a good perioperative antibiotic prophylaxis in renal transplantation.

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References

1. Canadian Multicenter Transplant Study Group (1986) A randomized clinical trial of cyclosporin in cadaveric renal transplantation: analysis at three years. N Engl J Med 314: 1219-1225
2. Condon RE, Friedhoff LT, Edmiston CE, Levinson B (1986) Aztreonam concentration in abdominal tissues and bile. Antimicrob Agents Chemother 29: 1101-1103
3. Creasy WA, Adamovics J, Dhruv R, Platt TB, Sugerman AA (1984) Pharmacokinetic interaction of aztreonam with other antibiotics. J Clin Pharmacol 24: 174-180
4. Donowitz GR, Mandell GL (1988) Drug therapy: beta-lactam antibiotics (part 2). N Engl J Med 318: 490-500
5. European Multicentre Trial Group (1983) Cyclosporin in cadaveric renal transplantation: one year follow-up of a multicentre trial. Lancet I: 986-989
6. Grundmann R, Kraume R (1984) Perioperative Antibiotikaprophylaxe und Wundinfektionsrisiko bei Nierentransplantation. Fortschr Med 102: 1199-1202
7. Harnett JD, Parfrey PS, Paul MD, Gault MH (1987) Erythromycin-cyclosporine interaction in renal transplant recipients. Transplantation 43: 316-318
8. Judson RT (1984) Wound infection following renal transplantation. Aust N Z J Surg 54: 223-224
9. Martell R, Heinrichs D, Stiller CR, Jenner M, Keown PA, Dupre J (1986) The effects of erythromycin in patients treated with cyclosporine. Ann Intern Med 104: 660-661
10. Muakkassa WF, Goldman MH, Mendez-Picon G, Lee HM (1983) Wound infections in renal transplant patients. J Urol 130: 17-19
11. Newman TJ, Dreslinski GR, Tadros SS (1985) Safety profile of aztreonam in clinical trials. Rev Infect Dis 7: 648-655
12. Novick AC (1981) The value of intraoperative antibiotics in preventing renal transplant wound infections. J Urol 125: 151-152
13. Pommer W, Krause PH, Berg PA, Neumayer HH, Mihatsch MJ, Molzahn M (1986) Acute interstitial nephritis and nonoliguric renal failure after cefaclor treatment. Klin Wochenschr 64: 290-293
14. Sattler FR, Schramm M, Swabb EA (1985) Safety of aztreonam and SQ in 26,992 elderly patients with renal insufficiency. Rev Infect Dis 7: 622-627
15. Termeer A, Hoitsma AJ, Koene RAP (1986) Severe nephrotoxicity caused by the combined use of gentamicin and cyclosporine in renal allograft recipients. Transplantation 42: 220-221
16. Tillegard A (1984) Renal transplant wound infection: the value of prophylactic antibiotic treatment. Scand J Urol Nephrol 18: 215-221
17. Tilney NL, Strom TB, Vineyard GC, Merrill JP (1978) Factors contributing to the declining mortality rate in renal transplantation. N Engl J Med 299: 1321-1325
18. Verhagen C, Pauw BE de, Witte T de, Holdrinet RSG, Janssen JTP, Williams KJ (1986) Ceftazidime does not enhance cyclosporine-A nephrotoxicity in febrile bone marrow transplantation patients. Blut 53: 333-339
19. Whiting PH, Thomson AW, Simpson JG (1983) Renal and hepatic function in rats treated with cyclosporin A in combination with gentamicin or cephalosporin antibiotics. Br J Exp Pathol 64: 693-701
20. Wilms H, Keller F, Hasselman J, Hantelmann W, Offermann G (1986) Antibiotikaprophylaxe bei Nierentransplantation. Z Urol Nephrol 79: 545-548