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Prophylactic isradipine treatment after kidney transplantation: a prospective double-blind placebo-controlled randomized trial

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Abstract There is evidence that calcium antagonists may have a beneficial effect on cyclosporine-induced nephropathy after transplantation. We treated 50 consecutive non-diabetic patients receiving their first cadaveric transplant with isradipine, a dihydropyridine calcium antagonist, or placebo in a double-blind, randomized, placebo-controlled trial. There were no significant differences between the two groups as regards age, weight, sex, HLA matching and ischaemic periods. To achieve optimal vasodilation, treatment was started intravenously 2 h before the transplantation procedure, and continued orally afterwards for 3 months. The immunosuppressive treatment included rabbit anti-thymocyte globulin on day 0, and oral cyclosporine from day 5. In both groups 7 patients had primary non-functioning grafts, but the incidence of never functioning kidneys due to vascular and thrombotic complications was significantly higher in the placebo group (0 vs 4 patients, $P < 0.05$). Hypertension was treated with oral labetolol in combination with guanfacine if necessary. In the placebo group antihypertensive medication had to be prescribed significantly more often (67% vs 33% of patients, $P < 0.05$), but resulted in similar blood pressure recordings in the two study groups. Cyclosporin A (CsA) plasma concentrations were also comparable but in the isradipine group a significantly higher dose of CsA was needed to achieve adequate levels (8.0 ± 0.5 vs 6.2 ± 0.5 mg/kg per day, $P < 0.01$). However, in the isradipine-treated patients creatinine clearance was significantly higher (66.1 ± 4.5 vs 55.6 ± 6.2 ml/min, $P < 0.05$) after 3 months. We conclude that isradipine is an effective antihypertensive agent after kidney transplantation. Isradipine ameliorates CsA-induced nephropathy and seems to protect against early postoperative vascular complications.

Key words Renal transplantation
Isradipine · Cyclosporin A
Graft function

Introduction

Graft survival after organ transplantation has significantly improved since the introduction of cyclosporin A (CsA) [1]. However, the nephrotoxicity of this drug often limits its use significantly. The deleterious effects of CsA are renal afferent arteriolar vasoconstriction, leading to a reduction of renal blood flow, and a decrease of glomerular filtration rate and filtration fraction. Hypertension is frequently observed and is caused by increased peripheral vascular resistance and decreased sodium excretion [2, 3].

Calcium antagonists of the dihydropyridine group have the potential to reverse the vasoconstrictory effects of CsA, increasing sodium excretion, and lowering blood pressure. It has been suggested that this category of drugs has an ameliorating effect on the development of CsA nephrotoxicity. Other possible benefits include inhibition of platelet aggregation, less frequent delayed graft function and enhanced immunosupppression [4–6]. However, no prospective double-blind placebo controlled studies are available on this subject and not all publications in this field report positive effects on early graft function. There may also be a substantial interaction between calcium antagonists and CsA pharmacokinetics, leading to significantly higher CsA blood levels [7, 8].

In the present prospective double-blind study kidney transplant recipients were prophylactically treated with isradipine, a dihydropyridine calcium antagonist with high affinity for vascular smooth muscle cells. Treatment was started intravenously before the transplantation procedure. The aim of the study was to investigate whether isradipine treatment improves graft function, influences the development of hypertension and interferes with CsA metabolism during the first 3 postoperative months.

Patients and methods

After approval had been given by the institutional Medical Ethics Committee 50 consecutive non-diabetic patients receiving their first post-mortem transplant were randomized either to treatment with isradipine (I) or placebo (P). Treatment in group I started 2 h before the operation, with a loading dose of 0.5 mg in a 30-min infusion, followed by a 48-h infusion of isradipine 0.06 mg/h. After 48 h oral isradipine capsules were started 2.5 mg b.i.d., and continued for 3 months. Group P was treated with saline infusion and vehicle capsules b.i.d. After 3 months all patients received placebo for another month to assess the reversibility of the observed effects.

The immunosuppressive regimen was the same in all patients and included a single shot of rabbit antithymocyte globulin (RIVM, Bilthoven, The Netherlands) 8 mg/kg intravenously on day 0, hydrocortisone intravenously 400 mg and 200 mg on days 0 and 1 respectively, followed by oral prednisone 15 mg from day 2 onwards. Oral CsA, in an initial dose of 4 mg/kg twice daily, was started on day 5, with later dose adjustments aiming at 12-h plasma trough levels of 50–75 mg/ml. CsA plasma levels were determined by a monoclonal assay (Cyclo Trac SP; Incstar, Stillwater, Minn. USA) at 1- to 4-week intervals. All patients were routinely heparinized for 48 h postoperatively.

Primary non-function was defined as the need to continue haemodialysis after the transplantation procedure. Delayed graft function, as an indicator of acute tubular necrosis, was diagnosed when patients were haemodialysed only temporarily, with adequate graft function during follow-up. All acute rejection episodes were biopsy proven. Patients with primary non-functioning grafts were excluded from further analysis, in order to allow a more reliable comparison between the two groups.

Blood pressure in the sitting and standing position was measured before the initiation of CsA, weekly during the 1st months and monthly up to the 4th month by an automated oscillometric method (AccuTorr II, Datascope Corp. Paramus, N.J., USA). Hypertension was treated in both groups with the adrenoceptor antagonist labetolol, in combination with the adrenergic neuron blocker guanfacine if necessary. In both groups no other calcium antagonist were used.

Haematological and biochemical determinations were performed by standard laboratory techniques. Creatinine clearance was calculated by standard methods. Laboratory evaluations were done daily during the hospitalization period and on day 21, 28, 56, 84 and 112 after transplantation.

The clinical characteristics of both groups were compared using Fisher's exact tests for nominal data and unpaired *t*-tests for interval data. The outcome of transplantation was compared using Fisher's exact test. The overall effect of isradipine compared to placebo was evaluated using two-way ANOVA with repeated measurements over time. When this yielded a significant *F*-value, further comparisons were made using the Student-Neumann-Keuls test.

Results are expressed as mean values ± standard error of the mean (SEM).

Results

After giving their informed consent 25 patients were included in each study group over a 14-month period. The main patient and donor characteristics are shown in Table 1. No significant differences were found with respect to age, weight, sex, ischaemic periods and HLA matching.

In each group one patient did not complete follow-up because of adverse events, in both cases palpitations and flushing. Both patients had experienced delayed graft function and were excluded from the final analysis.

In each study group seven patients had primary non-functioning kidneys (Table 2). In group p four of these patients had grafts that never functioned, while all primary non-functioning grafts in group I functioned adequately during follow-up ($P < 0.05$). All four patients with never-functioning kidneys underwent nephrectomy. All operation specimens showed extensive intravascular thrombosis, without evidence of technical failure. No immunoglobulin depositions indicating hyperacute or

Table 1 Baseline patient characteristics. None of the parameters was statistically significant different between the two groups. Mean values ± SEM

	Baseline patient characteristics	
	Isradipine	Placebo
Number	25	25
Gender (M/F)	17/8	19/6
Age (years)	46.6 ± 11.5	51.1 ± 13.8
Weight (kg)	68.5 ± 13.8	72.0 ± 14.1
Ischaemic periods		
cold (h)	28.5 ± 7.0	28.1 ± 6.7
1st warm (min)	0.6 ± 0.2	0.3 ± 0.1
2nd warm (min)	28.3 ± 7.2	28.0 ± 9.0
Mismatches		
HLA-A	0.88	0.72
HLA-B	0.60	0.80
HLA-DR	0.18	0.12
Treatment before transplantation		
Haemodialysis	20	15
Peritoneal dialysis	5	7
None	0	3
Donor characteristics		
Age (years)	40.5 ± 14.7	39.1 ± 14.2
Sex (M/F)	16/9	17/8
Multiorgan donor (Y/N)	16/9	14/11

Table 2 Early graft function and graft survival after 4 months and 1 year of follow-up

	Isradipine	Placebo
Total number of patients	25	25
Primary non-function	7	7
Acute tubular necrosis	7	3
Never functioning	0	4
Fourth-month graft survival	100%	84%
One-year graft survival	92%	76%

accelerated rejection were observed. Delayed graft function occurred in seven isradipine-treated and in three placebo-treated patients (NS).

The incidence of acute rejection episodes was similar, occurring in four patients in each group. All acute rejections were treated with high-dose prednisolone for 3 consecutive days or rabbit antithymocyte globulin, without subsequent graft loss. Graft survival after 4 months of follow-up was 100% in the I group versus 84% in the P group. One-year graft survival, after completion of trial follow-up, was 92% in the group versus 76% in the P group (NS) (Table 2).

Eighteen patients in both groups had immediate graft function and were included in further analyses of blood pressure, CsA metabolism and graft function.

Mean arterial blood pressure recordings showed no significant differences between the two groups in either the sitting or standing position at any time during follow-up. However, significantly fewer isradipine-treated patients had to be treated with the antihypertensive drugs mentioned above [6 (33%) versus 12 (67%) patients; $P < 0.05$]. During follow-up mean CsA plasma concentrations were similar in both groups (53.4 ± 5.3 vs 56.1 ± 7.1 ng/ml), despite the fact that group I received significantly higher doses of CsA per kilogram body weight (8.0 ± 0.5 vs 6.2 ± 0.5 mg/kg per day, $P < 0.05$) (Fig. 1).

Graft function was significantly better in the I group. Mean serum creatinine was 148.4 ± 13.8 μmol/l in the I group versus 212.7 ± 23.1 μmol/l in the P group after 10 days ($P < 0.01$). This difference persisted throughout 3 months of follow-up, the isradipine-treated patients

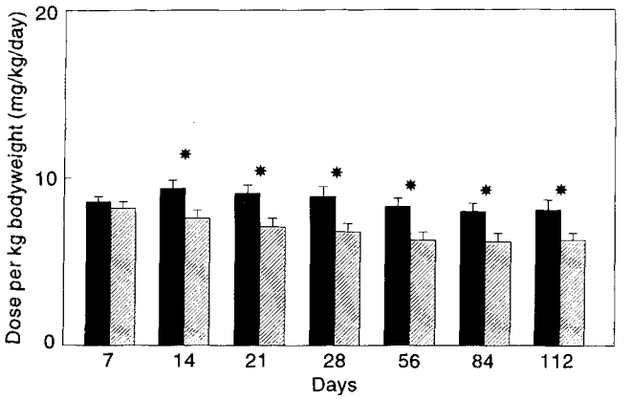

Fig. 1 Daily cyclosporine dose per kilogram body weight (mean values ± SEM) in isradipine-treated patients (*solid bars*) and palcebo-treated patients (*hatched bars*). * $P < 0.05$

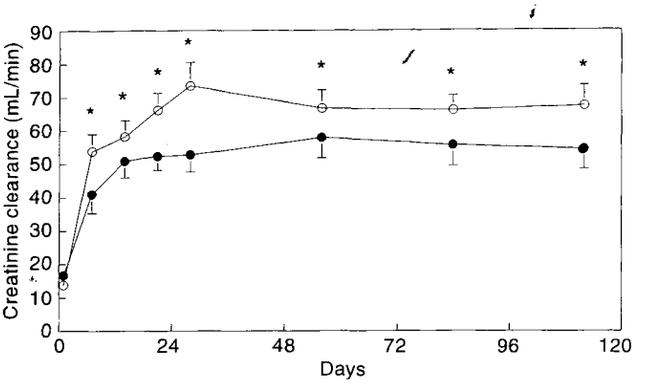

Fig. 2 Creatinine clearance (mean values ± SEM) during the first 4 post-transplant months in the isradipine-treated patients (*open circles*) and the placebo-treated patients (*closed circles*) * $P < 0.05$

having significantly lower serum creatinine levels (142.0 ± 11.9 vs 164.0 ± 10.8 μmol/l, $P < 0.05$) and higher creatinine clearances (66.1 ± 4.5 vs 55.6 ± 6.2 ml/min, $P < 0.05$) (Fig. 2).

None of the studied parameters changed significantly during the 4th month of follow-up, when all patients received placebo treatment.

Discussion

CsA is generally accepted as the first-choice immunosuppressant because of its ability to improve graft survival by about 15–20% when compared to azathioprine [8]. Several investigators have made attempts to mitigate the acute and chronic nephrotoxicity of CsA, which often limits its use. Calcium channel blockers have the potential to partially antagonize these effects [2, 9].

In this prospective study we started isradipine treatment 2 h before the transplantation procedure. In some other studies calcium antagonists have been used prophylactically, though treatment was not started intravenously. There was an equal number of delayed functioning grafts in both groups, but we found a significantly higher rate of never-functioning kidneys in the placebo-treated group, all leading to nephrectomy. All nephrectomy specimens showed extensive intravascular thrombosis without evidence of rejection or technical failure. These findings suggest that the extent of ischaemic damage was smaller with isradipine treatment. The use of anti-T-cell globulin increases the incidence of early thrombotic complications. It has been reported that calcium antagonists have an inhibiting effect on platelet aggregation. This and the increased renal blood flow and glomerular filtration rate caused by calcium antagonists may have prevented intravascular thrombosis. Several authors have reported a protective effect of calcium antagonists with regard to the occurrence of acute tubular necrosis [4, 9]. This is probably mediated by the inhibition of calcium influx into the tubular cells during ischaemia [10]. However, it seems that administration of calcium antagonists before the ischaemic period is necessary to achieve maximum benefit. A reduced risk of primary nonfunction has bee reported when diltiazem is administered preoperatively to either donor or recipient, or added to the preservation solution [4].

To make a more reliable comparison of the effects of isradipine beyond the early postoperative phase, patients with immediate graft function were evaluated with respect to blood pressure, CsA metabolism and graft function during follow-up. It has been demonstrated previously that calcium antagonist treatment leads to improved graft function [4–6] though double-blind studies have not been carried out. Our data showed significantly better graft function with isradipine 10 days after the transplantation. This difference persisted during the whole follow-up period. Improvement of graft function was delayed, and stabilized at a higher serum creatinine level in the placebo group. This suggests that early graft function is mainly determined by the extent of ischaemic damage, which seems to be limited by isradipine. Hypertension is a major problem in clinical organ transplantation, affecting up to 80% of CsA-treated patients [11, 12]. The mechanism by which CsA causes hypertension is not completely clear. The metabolism of several mediators, e.g. prostaglandin I_2, thromboxane A_2 and endothelin-1, is altered by CsA treatment. It has been demonstrated that CsA impairs endothelial functions, which is probably one of the underlying mechanisms of CsA toxicity. CsA also increases calcium influx into vascular smooth muscle cells, leading to increasing vascular tone. Calcium antagonists may interfere with several of these mechanisms, which are mostly calcium dependent. Calcium antagonists have shown to be effective against CsA-induced hypertension [9, 11, 13]. Isradipine treatment led to adequate blood pressure control in the majority of patients, while in the placebo group 66% of patients had to be treated for hypertension with one or more drugs. Overall blood pressure control was similar in the two groups, which suggests that, apart from hypertension other factors are important determinants of long-term graft function.

There is evidence that calcium antagonist treatment interferes with CsA metabolism, leading to higher blood CsA levels [7, 8, 14]. For the whole group of dihydropyridines there are conflicting data on this subject. Surprisingly, our data seem to indicate that isradipine treatment enhances CsA metabolism, as higher daily doses per kilogram body weight were required to reach similar plasma levels. However, other investigators have found no influence of isradipine treatment on CsA pharmacokinetics [15, 16], and more detailed pharmacokinetic studies are necessary to clarify this issue.

The number and severity of rejection episodes was not different between the two groups. The relatively low incidence of acute rejection seems to be related to the use of antithymocyte globulin. Some authors have reported a significantly reduced incidence of acute vascular rejection in patients treated with calcium antagonists, which might be explained by higher CsA blood levels caused by the interference of calcium antagonists with CsA metabolism.

In summary, the administration of isradipine leads to a decreased incidence of primary non-function and better graft function after 3 months of follow-up. Isradipine treatment controlled hypertension adequately in the majority of patients. Our data also suggest enhancement of CsA metabolism during isradipine therapy.

References

1. European Multicentre Trial Group (1987) Cyclosporine in cadaveric renal transplantation: 5-year follow-up of a multicentre trial. Lancet II:506–509
2. McNally PG, Feehally J (1992) Pathophysiology of cyclosporin A nephrotoxicity: experimental and clinical observations. Nephrol Dial Transplant 7:791–804
3. Myers BD, Sibley R, Newton L, et al. (1988) The long-term course of cyclosporine-associated chronic nephropathy. Kidney Int 33:590–600
4. Wagner K, Albrecht S, Neumayer H-H (1987) Prevention of posttransplant acute tubular necrosis by the calcium antagonist diltiazem: a prospective randomized study. Am J Nephrol 7:287–289
5. Palmer BF, Dawidson I, Sagalowsky A, Sandor Z, Lu CL (1991) Improved outcome of cadaveric renal transplantation due to calcium channel blockers. Transplantation 52:640–645
6. Harper SJ, Moorhouse J, Veitch PS, et al. (1992) Improved immediate graft function with nifedipine in cyclosporine-treated renal allograft recipients – a randomized prospective study. Transplantation 54:742–743
7. Pedersen EB, Sorensen SS, Eiskjaer H, Skovbon H, Thomsen K (1992) Interaction between cyclosporine and felodipine in renal transplant recipients. Kidney Int 41 [Suppl 36]: S82–S86
8. McNally P, Mistry N, Idle J, Walls J, Feehally J (1989) Calcium channel blockers and cyclosporine metabolism. Transplantation 48:1071
9. Loutzenhiser R, Epstein M (1985) Effects of calcium antagonists on renal hemodynamics. Am J Physiol 249:F619–F629
10. Bonventre JV (1993) Mechanisms of acute renal failure. Kidney Int 43:1160–1178
11. Chapman JR, Marcen R, Arias M, Raine AEG, Dunnill MS, Morris PJ (1987) Hypertension after renal transplantation. A comparison of cyclosporine and conventional immunosuppression. Transplantation 43:860–814
12. Editorial (1988) Cyclosporine hypertension. Lancet II:1234
13. Kirk AJB, Omar I, Bateman DN, Dark JH (1989) Cyclosporine-associated hypertension in cardiopulmonary transplantation. The beneficial effect of nifedipine on renal function. Transplantation 48:428–430
14. Lindholm A, Henricsson S (1987) Verapamil inhibits cyclosporin metabolism. Lancet I:1262
15. Berg KJ, Holdaas H, Endresen L, et al. (1991) Effects of isradipine on renal function in cyclosporin-treated renal transplanted patients. Nephrol Dial Transplant 6:725–730
16. Martinez F, Pirson Y, Wallemacq P, Van Ypersele de Strihou C (1991) No clinically significant interaction between ciclosporin and isradipine. Nephron 59:658–659