Safety, Tolerability, and Pharmacokinetic Actions of Diltiazem in Pediatric Liver Transplant Recipients on Cyclosporine

Mohammed Al Edreesi, Gilles Caillé,† Claire Dupuis,‡ Yves Théoret,† and Khazal Paradis**

Thirty-two children who had undergone liver transplantation were paired according to their post-transplantation duration, renal function, and diagnoses when possible and randomized either to continue nifedipine (NIF group) or switch to diltiazem (DIL group), in addition to continuing their usual immunosuppressive medications. The cases were followed prospectively regarding diltiazem tolerance, cyclosporine dose requirements, effect on cyclosporine kinetics, diltiazem kinetics, as well as effect on renal function. Diltiazem was well tolerated at a dose of 3 mg to 6.4 mg/kg/day (max 180 mg/day) with infrequent self-limited mild side effects. Cyclosporine daily dose was reduced by a mean of 36.7% and 38.3% at 3 and 6 months, respectively, in the DIL group to achieve target trough cyclosporine levels without modifying liver function. No significant difference in renal function was observed after 3 to 6 months in either group based on blood urea nitrogen and creatinine levels and glomerular filtration rate by the DTPA method. Diltiazem appears to be well tolerated in children and allows for substantial dose reductions of CSA without apparent effects on liver graft function.

Cyclosporin A (CSA) remains one of the cornerstones of maintenance immunosuppression therapy in solid organ transplantation. Its use is associated with high cost as well as potential side effects. CSA-induced nephrotoxicity is potentially a serious complication that may lead to progressive loss of renal function and eventually, although rarely, renal insufficiency.[1,2]

CSA is metabolized in the liver by a cytochrome P450 III A enzyme system that may be induced or inhibited by several compounds.[3,4] Commonly used medications after organ transplantation include inhibitors of the hepatic cytochrome P450 III A such as corticosteroids, erythromycin, ketoconazole, and diltiazem.

Diltiazem, a benzothiazepine derivative, is a calcium channel blocker that is used primarily in adults as an antihypertensive and anti-angina agent.[5] More recently it has been used as a CSA-sparing agent in adults after heart and kidney transplantations[6-8] with consequent reduction in the CSA cost. Being a calcium antagonist, diltiazem may have a nephroprotective effect, in part through its vasodilator action and probably by other mechanisms as well.[9-11] In experimental animals, in vitro studies, as well as a few human studies, it was found that diltiazem may also exert an immunomodulatory effect that favors graft tolerance and possibly lowers the risk of rejection.[12-15]

Diltiazem has been rarely used in the pediatric age group. Long-term use (up to 32 months) has been reported in children with Duchenne muscular dystrophy with no demonstrable side effects.[16] Few other scattered reports have shown its use in supraventricular tachycardia and pulmonary hypertension.[17] There is no available information in the English literature regarding use of diltiazem in pediatric transplantation or in liver transplantation. In view of the previously mentioined potential benefits of diltiazem in the transplantation population, we carried out a paired, randomized, prospective study in 32 children who had undergone liver transplantation with particular attention to diltiazem tolerance, kinetics, and CSA-diltiazem interaction, as well as short-term impact on renal function.

*From the *Montreal Pediatric Liver Transplant Program, Hôpital Ste-Justine; †Department of Pharmacology, Université de Montreal; and ‡Department of Biochemistry, Hôpital Ste-Justine, Montreal, Quebec, Canada.*

Supported by the Erin Walker Liver Transplant Fund, Montreal, Quebec, Canada.

Address reprint requests to: Khazal Paradis, MD, Pediatric Liver Transplant Program, Hôpital Ste-Justine, 3175 Côte Ste-Catherine, Montreal, Quebec H3T 1C5, Canada.

1074-3022/95/0106-0008$3.00/0

Methods

Thirty-two pediatric liver transplant recipients interested in participating in the study were matched and paired according to pretransplantation diagnosis, posttransplantation duration and glomerular filtration rate (GFR) using the DTPA method.[18] The protocol was approved by the institutional ethics committee and informed parental consent was obtained. Patients less than 2 months posttransplantation, with chronic liver rejection, or cardiac arrhythmia were excluded from the study. One patient of each pair was then randomized to either continue their current calcium-channel blocker therapy (nifedipine [NIF group]), or to begin diltiazem (DIL group). In view of the expected interaction of diltiazem with cyclosporine, those children randomized to the DIL group, had their usual CSA dose reduced by 20% to 30% on initiation of diltiazem therapy. Diltiazem was administered at a dose of 3 to 6.4 mg/kg/day (maximum 180 mg/day) using 30- or 60-mg controlled release tablets, taken concurrently with their CSA dose. CSA levels and blood biochemistries (see later) were drawn weekly until a desired steady-state CSA trough level was obtained. For both DIL and NIF groups, the usual monthly CSA levels were then obtained in conjunction with liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transpeptidase [GGT]), blood urea nitrogen (BUN), creatinine, complete blood count (CBC), and electrolytes. Targeted CSA trough levels were 150 to 175 ng/mL (monoclonal radio immunoassay on whole blood) at 2 to 4 months posttransplantation, and 90 to 150 ng/mL thereafter. The only other change in maintenance immunosuppressive therapy performed during the study was a continued steroid tapering with time in both groups.

An electrocardiogram was performed at initiation of the study, at 1 week and 3 months after beginning diltiazem, and once during the study period in the NIF group. Blood pressure was recorded weekly for a month in the DIL group and monthly thereafter for both groups. Parents of both groups were instructed to maintain a daily diary of any symptoms and to call for any untoward reaction. CSA kinetics were performed before initiation of diltiazem and repeated after 3 months of diltiazem therapy by measuring trough and hourly CSA levels by micromethod after ingestion of their usual CSA and diltiazem doses, with the use of an indwelling heparin-lock. At the 3rd month kinetic study, blood was simultaneously obtained for measurement of diltiazem levels. Plasma for diltiazem kinetics was centrifuged within 30 minutes and immediately frozen at −80°C. Measurement of the parent compound and the two metabolites, desacetyl diltiazem (DAD) and *N*-monodemethyl diltiazem (MA), were carried out by high-performance liquid chromatography as previously described.[19]

Renal function was evaluated with a biannual DTPA-GFR, and monthly measurement of BUN and creatinine. Statistical analyses were carried out using the χ^2 test for diagnoses; *t*-test for comparison of DIL and NIF groups with regards to DTPA GFR, BUN, creatinine, entry, and 6 month CSA dose; paired *t*-test for 6 month CSA dose versus entry CSA dose, area under the curve (AUC) for CSA at entry and 3 months after diltiazem, and CSA peak levels at entry and 3 months; repeated ANOVA for CSA levels at each month.

Results

Patient Characteristics

There were no significant differences between the two groups with respect to pretransplantation diagnosis, age, gender, posttransplantation duration, DTPA-GFR, (Tables 1 and 2), and immunosuppression (Table 3). In the NIF group, two patients dropped out (one rejected the result of randomization and the second could not comply with the protocol) and another two patients were excluded (one had progression of posttransplantation complications and the second was noncompliant with her medications). Fourteen patients in the DIL group and all 12 in the NIF group were treated with CSA three times daily, whereas 2 in the DIL group were on a twice daily regimen.

Tolerance of Diltiazem

Two children, both less than 4 years old, received their diltiazem crushed with some juice. Diltiazem was well tolerated with mild transient side effects reported in three children. One patient had two episodes of scotomata without loss of consciousness in the first 3 days of starting diltiazem, which were precipitated by sudden changes in posture and lasted for few seconds. These resolved without changing the diltiazem dose (both electrocardiogram (ECG) and blood pressure were normal). In the other two patients, one had transient abdominal pain and the second was observed to have hand tremors. In the NIF group, one patient reported hand tremors and one had transient abdominal pain. Blood pressure control was comparable in both groups with one

Table 1. Study Population

Diagnosis	Diltiazem (n = 16)	Nifedipine (n = 16)
Tyrosinemia	5	5 (1*)
Biliary atresia	5	6 (2*)
North American Indian cirrhosis	1	1
Byler's disease	0	2
Wilson's disease	0	1
Autoimmune hepatitis	1	0
Fulminant hepatitis	1	0
Hyperoxaluria type 1	1	0
Glycogen storage disease	1	0 (1*)
Alagille syndrome	1	0

*Withdrawals from study.

Table 2. Study Population

	Diltiazem Group (n = 16)	Nifedepine Group (n = 12)
Mean age	7 yr 11 mos (2 yr 3 mos to 18 yr)	8 yr 5 mos (1 yr 11 mos to 14 yr)
Gender (male/female)	6/9	4/8
Posttransplantation duration	41 mos (3.5-103)	38.8 mos (2 to 91)
GFR by DTPA (mL/min/1.73 m^2)		
>80	12	9
≤80	4	3

hypertensive patient (systolic and/or diastolic BP greater than 95th centile for age for three consecutive measurements) in each group. Serial ECGs showed no change in the PR interval.

Mildly elevated ALT (> 1.5 upper limit of normal) was observed at study entry in two patients in the DIL group. On follow-up, one patient's level normalized, whereas the other remained elevated with no defined etiology despite investigation including a liver biopsy. One patient in the DIL group developed transient liver enzyme elevation (ALT 1.6 and AST 2.2 times upper limit of normal), which spontaneously normalized over a 4-week period. All patients in the NIF group continued to have normal ALT levels during the study period. One patient in the DIL group developed a rejection episode 10 months after starting diltiazem with consequent low CSA levels (62 ng/mL) probably because of omitting his diltiazem dose repeatedly. The patient had been 6 years out from transplantation, with no steroids for 3 1/2 years, and responded to oral steroid recycling. He was subsequently weaned off steroids within 8 weeks with normal liver enzymes.

Interaction With Cyclosporine

In the DIL group the CSA dose was found to be reduced by 38.3% (range, 21% to 51.1%), at the end of 6 months, as compared with their entry dose ($P \leq .001$). No significant change in the CSA dose was observed in the NIF group for the duration of the study period.

There were no significant differences in CSA trough levels for both groups at each month of the study with means of 139.1 ng/mL DIL and 139.8 ng/mL NIF at 6 months) (Tables 4 and 5). CSA dose reduction was mainly achieved during the first 4 weeks of starting diltiazem therapy.

Cyclosporine Kinetics

At entry into the study, time to CSA peak level (Tmax) was 2.5 hours (1 hour to 5 hour), and CSA peak level (Cmax) was 450.6 ng/mL (89 to 1094 ng/mL). After three months of diltiazem administration, CSA Tmax was 1.9 hour (1 to 5 hours, NS), and CSA Cmax was 329.6 ng/mL (134-598 ng/mL, $P = .004$). The AUC for CSA was 1674.6 ng/mL before starting diltiazem and 1445.4 ng/mL while receiving diltiazem treatment ($P = .03$).

Diltiazem Kinetics

In the patients taking their diltiazem three times daily, the Cmax was 223.1 ng/mL (range, 68.3 to 432 ng/mL), Tmax 2.7 hour (1 to 7 hours), Cmin 85.5 ng/mL (39.4 to 175.7 ng/mL), and the AUC 926.4 ng · h/mL (410 to 1737.6 ng · h/mL). For the other two patients on twice daily diltiazem, Cmax was 224.1 ng/mL (190.4 to 428.8 ng/mL), Tmax 3.5 hours (2 to 5 hours), Cmin 51 ng/mL (46.5 to 55.4

Table 3. Immunosuppression During the Study

	Diltiazem Group		Nifedipine Group	
Medication	No. of Patients (n = 16)	Average Dosage (mg/kg/d)	No. of Patients (n = 12)	Average Dosage (mg/kg/d)
Cyclosporine	16	3.7 (1.6-6.9)	12	5.9 (3.1-9)
Azathioprine	14	1.19 (0.58-1.78)	11	1.15 (0.30-1.78)
Prednisone				
Daily	4	0.19 (0.06-0.31)	2	0.21 (0.18-0.24)
Alternate days	7	0.11 (0.06-0.23)	7	0.21 (0.05-0.37)
None	5	0	3	0

Table 4. Change in Cyclosporine Dose

	Mean CSA Dosage mg/kg/d (range)		
	At Study Entry	At 3 Months	At 6 Months
Diltiazem group	5.8 (2.6-9.6)	3.7 (1.6-6.9)	3.6 (1.6-6.8)
Nifedipine group	5.7 (3.1-8.6)	5.9 (3.1-9)	5.9 (3.1-9.6)
P	NS	≤.001	≤.001

ng/mL) and the AUC 1196 ng · h/mL (1152.3 to 1239.7).

Elimination half life ($T_{1/2el}$) could not be calculated in 4 patients (because of lack of evidence of elimination during the 8-hour period of sampling), whereas $T_{1/2el}$ was 3.62 hours (1.9 to 13.64 hours) in the remaining 12 patients.

MA and DAD peak levels were 17.9 ng/mL (6.1 to 37.9) ng/mL and 65.5 ng/mL (30 to 95.8 ng/mL), respectively, and the ratio to the parent compound was 28% and 7.6%, respectively.

Renal Function

No significant differences in BUN were found between the DIL group (6.17 ± 1.74) and NIF group (5.64 ± 2.11). Similarly, monthly creatinine levels did not vary significantly between groups, and DTPA GFR at 6 months was not different in either group for entry values.

Discussion

Several investigators have studied the interaction between CSA and other medications.[3,4] These medications can either inhibit (eg, steroids, erythromycin, diltiazem, and ketoconazole) or induce (eg, rifampicin, phenytoin, and carbamazepine) CSA metabolism by interfering with hepatic cytochrome P450 III A and consequently either increasing or decreasing the CSA plasma levels. Both dilitazem and ketoconazole have been used as CSA-sparing agents.[6,7,20] Long-term use of ketoconazole in the immunosuppressed patient may theoretically result in the selection of resistant fungal strains.

Diltiazem has been used in adults primarily as an antihypertensive agent as well as treatment of angina because of its vasodilator effect.[5,21] During the period of the study, it appeared to be as effective as nifedipine at controlling hypertension in this pediatric population. More recently, diltiazem has been added to the CSA-based immunosuppression as a CSA-sparing agent in the adult transplant population,[5-8] and this effect appears to be stable and safe in our pediatric transplantation population as well.

Diltiazem has been rarely used in the pediatric age group,[16,17] and to our knowledge, no report of its use in liver transplantation has been published. In our patients, the use of diltiazem was associated with infrequent, transient mild side effects that were not different from the control group. None of our patients had any PR interval abnormality including the two children who were taking their diltiazem in the "crushed tablet" form. The more rapid absorption of diltiazem in these circumstances can theoretically cause atrioventricular conduction delay,[22] something which did not happen in our patient population.

CSA dose reductions ranging from 20% to 50% have been reported in studies in adults receiving diltiazem after heart or kidney transplantation.[6-8] Similarly in our pediatric liver transplantation population, an average 38% reduction in the original daily CSA dose was observed after 6 months of starting diltiazem treatment. The CSA peak levels as well as AUC for CSA were slightly but significantly lower

Table 5. CSA Trough Levels

	Mean CSA Trough ng/mL (range)		
	At Study Entry	At 3 Months	At 6 Months
Diltiazem group	142.2 (90-259)	154.7 (100-224)	139.1 (98-226)
Nifedipine group	140.9 (108-188)	134.9 (71-180)	139.8 (98-193)

P = NS for the study period.

while administering diltiazem despite maintaining comparable trough CSA levels. Avoiding higher CSA peak levels may possibly translate into less nephrotoxic effect in the long term, but did not affect renal function in this short-term study.

Diltiazem is well absorbed from the gastrointestinal tract; however, because of extensive first-pass metabolism, the absolute bioavailability of diltiazem after single doses ranges from 15% to 74%.[23-25] During chronic administration of diltiazem, the mean bioavailability increases from 38% to 90% indicating saturation of hepatic first-pass metabolism.[24] This did not appear to affect the stability of CSA metabolism in our pediatric population, as almost all CSA dose adjustments occurred within the first month of initiating diltiazem treatment; however, the wide range of peak diltiazem levels observed probably reflects the well-known interindividual variability in diltiazem absorption and metabolism.

The diltiazem pharmacokinetics in our pediatric liver transplantation population revealed a lower Cmax to that reported in adult angina patients (223.1 ng/mL *v* 409 ng/mL, respectively), and a comparable Tmax (2.7 hours *v* 2.76 hours, respectively). The $T_{1/2el}$ of 3.75 hours in our patients is similar to the one reported in adult studies with $T_{1/2el}$ usually between 2 and 6 hours.

Diltiazem is extensively metabolized by the liver with only 0.1% to 4% of the oral dose excreted in the urine as the parent drug.[26] Diltiazem metabolism begins with deacetylation followed by *N*- and *O*-demethylation through the oxidative cytochrome P-450 enzyme system; the phenolic metabolites are conjugated in part with glucuronides or sulfates. In humans, the most important metabolites detected in plasma are, in the following order, MA, DAD, and M2.[27] The pharmacological activity of these metabolites as vasodilators is poorly defined, but it is thought to be only 10% to 20% of the parent drug's activity with the MA more active than the DAD metabolite.[27]

In our patients, both MA and DAD constituted 28% and 7.6%, respectively, of the parent drug level, comparable to the findings in adults, implying that the metabolic breakdown of diltiazem is similar in children and adults. The therapeutic vasodilator effect of diltiazem in hypertensive and angina patients is present at levels between 100 to 200 ng/mL.[21] The presence of a therapeutic diltiazem level in our population is difficult to define as our measurable therapeutic effect was the CSA dose reduction, and moreover, a significant CSA dose reduction was achieved even in those children with relatively low diltiazem trough levels. The hypertensive child in the diltiazem group had a supposedly therapeutic trough level of 121.2 ng/mL.

The one episode of rejection observed in a diltiazem-treated patient emphasizes the importance of compliance as the resultant subtherapeutic CSA levels observed when diltiazem is stopped increases the risk for rejection. In one study, the discontinuation of diltiazem was associated with twice the incidence of renal graft rejection when compared with discontinuation of nifedipine in a control group.[28] Other investigators have shown that using diltiazem in the early post-renal transplantation period may be associated with lower incidence of rejection.[11,12]

In conclusion, diltiazem is well tolerated in pediatric liver transplant recipients, and when combined to the CSA-based immunosuppressive regimen, allowed for significant reduction in daily CSA requirements with consequent favorable economic outcome. However, the inhibitory effect of diltiazem on CSA metabolism is reversible, and noncompliance may result in an increased risk of rejection if the CSA dose is not adjusted. The long-term effect of associating diltiazem to CSA immunosuppression on renal function requires further study.

Acknowledgment

We thank Caroline Godbout for statistical analyses and Danielle St-Cyr Huot for manuscript preparation.

References

1. Paul A, Levy GA, Greig PD. Balancing cyclosporin A nephrotoxicity and rejection late after adult liver transplantation. Transplant Proc 1993;25:2664-2665.
2. Iwatsuki S, Esquivel CO, Klintmalm GB, Gordon RD, Shaw BW Jr, Starzl TE. Nephrotoxicity of cyclosporine in liver transplantation. Transplant Proc 1985;17:191-195.
3. Pichard L, Fabre I, Fabre G, Domergue J, Saint Aubert B, Bouard G, et al. Cyclosporine A drug interactions: Screening for inducers and inhibitors of cytochrome P 450 (cyclosporine A oxidase) in primary cultures of human hepatocytes and in liver microsomes. Drug Metab Dispos Biol Fate Chem 1990;18:595.
4. Henricsson S, Lindholm A. Inhibition of cyclosporine metabolism by other drugs in vitro. Transplant Proc 1988;20:569-571.
5. Kiowski W, Linder L, Bühler FR. Arterial vasodilator and antihypertensive effects of diltiazem. J Cardiovasc Pharmacol 1990;16:S7-S10.
6. Bourge RC, Kirklin JK, Naftel DC, Figg WD, White-

Williams C, Ketchum C. Diltiazem-cyclosporine interaction in cardiac transplant recipients: Impact on cyclosporine dose and medication costs. Am J Med 1991;90: 402-404.
7. McCauley J, Ptachcinski RJ, Shapiro R. The cyclosporine-sparing effects of diltiazem in renal transplantation. Transplant Proc 1989;21:3955-3957.
8. Kohlhaw K, Wonigeit K, Frei U, Oldhafer K, Neyman K, Pichlmayr R. Effect of the calcium channel blocker diltiazem on cyclosporine A blood levels and dose requirements. Transplant Proc 1988;20:572-574.
9. Frei U, Harms A, Bakovic-Alt R, Pichlmayr R, Koch KM. Calcium channel blockers for kidney protection. J Cardiovasc Pharmacol 1990;16:S11-S15.
10. Macdonald P, Keogh A, Marshman D, Richens D, Harvison A, Kaan A, et al. Two year follow up of a prospective randomized study of diltiazem coadministration with cyclosporine after heart transplantation. J Heart Lung Transplant 1993;12:S80.
11. Alcaraz A, Oppenheimer F, Talbot-Wright R, Fernandez-Cruz L, Manalich M, Garcia-Pages E, et al. Effect of diltiazem in the prevention of acute tubular necrosis, acute rejection, and cyclosporine levels. Transplant Proc 1991;23:2383-2384.
12. Kunzendorf U, Walz G, Brockmoeller J, Neumayer HH, Jochimsen F, Roots I, et al. Effects of diltiazem upon metabolism and immunosuppressive action of cyclosporine in kidney graft recipients. Transplantation 1991; 52:280-284.
13. Dumont L, Chen H, Daloze P, Xu D, Garceau D. Immunosuppressive properties of the benzothiazepine calcium antagonists diltiazem and clentiazem, with and without cyclosporine, in heterotopic rat heart transplantation. Transplantation 1993;56:181-184.
14. Mandreoli M, Esposti ED, Cocchi R, Fabbri A, Gurrini L, Fusaroli M. Do calcium channel blockers have any influence on the immunological status of renal graft recipients on cyclosporine therapy? Am J Nephrol 1990;10:58-60.
15. Chrysostomou A, Walker RG, Russ GR, D'apice AJF, Kincaid-Smith P, Mathew TH. Diltiazem in renal allograft recipients receiving cyclosporine. Transplantation 1993; 55:300-304.
16. Bertorini TE, Palmieri GMA, Griffin JW, Igarashi M, McGee J, Brown R, et al. Effect of chronic treatment with the calcium antagonist diltiazem in Duchenne muscular dystrophy. Neurology 1988;38:609-613.
17. Kasian GF, Ninan A, Duncan WJ, Bingham WT, Mersal A, Tyrrell MJ, et al. Treatment of pulmonary hypertension with diltiazem in a child with bronchopulmonary dysfunction. Can J Cardiol 1988;4:181-184.
18. Waller DG, Keast CM, Fleming JS, Ackery DM. Measurement of glomerular filtration rate with technetium-99m DTPA: Comparison of plasma clearance technique. J Nucl Med 1987;28:372-375.
19. Caillé G, Dubé LM, Théoret Y, Varin F, Mousseau N, McGilveray IJ. Stability study of diltiazem and two of its metabolites using a high performance liquid chromatographic method. Biopharm and Drug Dispos 1989;10: 107-114.
20. Patton PR, Brunson ME, Pfaff WW, Howard RJ, Peterson JC, Ramos EL, et al. A preliminary report of diltiazem and ketoconazole: Their cyclosporine-sparing effect and impact on transplant outcome. Transplantation 1994;57:889-892.
21. Hung J, Hackett PL, Gordon SPF, Ilett KF. Pharmacokinetics of diltiazem in patients with unstable angina pectoris. Clin Pharmacol Ther 1988;43:466-470.
22. Fu M, Hung J-S, Yeh S-J, Lin F-C, Hsu RS, Wu D. Pharmacokinetics and pharmacodynamic effects of aqueous diltiazem in healthy humans. J Clin Pharmacol 1989;27:106-110.
23. Piepho RW, Blaedow DC, Lacs JP, Runser DJ, Dimmit DC, Browne RK. Pharmacokinetics of diltiazem in selected animal species and human beings. Am J Cardiol 1982;49:525-528.
24. Smith MS, Verghese CP, Shand DG, Pritchett ELC. Pharmacokinetic and pharmacodynamic effects of diltiazem. Am J Cardiol 1983;51:1369-1374.
25. Hermann P, Rodger SD, Remoncs G, Thenot JP, London DR, Morselli PL. Pharmacokinetics of diltiazem after intravenous and oral administration. Eur J Clin Pharmacol 1983;24:349-352.
26. Dubruc C, Hermann C, Thiercelin P, Thernot JF, Thebault JP, Blatrix JJ, et al. Pharmacokinetics of diltiazem after oral and intravenous administration. Biopharm Pharmacokinet Eur Congr 1984;2:584-590.
27. Chaffman M, Brogden RN. Diltiazem: A review of its pharmacological properties and therapeutic efficacy. Drugs 1985;29:387-454.
28. Wagner K, Henkel M, Heinemeyer G, Neumayer H-H. Interaction of calcium blockers and cyclosporine. Transplant Proc 1988;20 (Suppl 2):561-568.