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Pharmacokinetic Drug-Drug Interaction of Calcium Channel Blockers With Cyclosporine in Hematopoietic Stem Cell Transplant Children

Elodie Bernard, PharmD[1], Sylvain Goutelle, PharmD[2], Yves Bertrand, MD[1], and Nathalie Bleyzac, PharmD[1,2]

Abstract

Background: Cyclosporine (CsA) is frequently responsible for hypertension in bone marrow transplant children. Calcium channel blockers (CCBs) are considered to be the best treatment for CsA-induced hypertension, but they may alter the exposure and the effect of CsA by inhibiting the CYP3A4 pathway of CsA metabolism or P-gp. However, the inhibitory effect on CYP3A4 may vary among CCBs. **Methods:** This study aimed to quantify the pharmacokinetic drug-drug interaction between CsA and nicardipine, amlodipine, and lacidipine. In all, 51 children who received CsA and CCB concomitantly were included. **Results:** Dose-normalized CsA trough blood concentrations significantly increased in patients treated with nicardipine and amlodipine, whereas they remained stable in patients treated with lacidipine. **Conclusions:** Because lacidipine appears to have no effect on CsA exposure, it may be the best option among CCBs for treating high blood pressure caused by CsA in children.

Keywords

calcium-channel blockers, cyclosporine, bone marrow transplantation, drug interactions, pediatrics

Background

High blood pressure is a frequent adverse effect of immunosuppressive therapy by cyclosporine (CsA) in hematopoietic stem cell transplantation (HSCT).[1] There are several mechanisms involved in the pathogenesis of CsA-induced hypertension, but the main alteration is a renal vasoconstriction resulting from endothelium disorders.[2-4] The increase in intracellular calcium caused by CsA plays an essential role in the genesis of vasoconstriction.[5] As a consequence, calcium channel blockers (CCBs) are viewed as the first option to treat high blood pressure caused by CsA.[6]

Among the numerous CCBs on the market, only nicardipine is available for intravenous (IV) administration, and it is generally used in children when rapid action is needed. All other CCBs are given orally, with amlodipine being the most frequently used CCB in children.[7-10]

CCBs are metabolized by cytochrome P450 3A4 enzymes (CYP3A4) and also have an inhibitory effect on CYP3A4, which varies from one agent to another.[11-13] Inhibition of CYP3A4 by CCBs may lead to a reduced clearance of coadministered drugs also metabolized by CYP3A4 such as CsA, which is commonly used to prevent graft-versus-host disease (GVHD) in HSCT. Indeed, CsA is mainly metabolized by liver and intestinal CYP3A4 and is also a P-glycoprotein substrate.[14] Among the available CCBs, nicardipine has been shown to have the strongest inhibition potential on CYP3A4, followed by lercanidipine, cilnidipine, nimodipine, and amlodipine.[13] Among the weakest CYP3A4 inhibitors, lacidipine is the only one available in France (not in the United States) as a suitable formulation for pediatric use (tablets with immediate release can be crushed to prepare low-dosage capsules).[13]

Objectives

For the reasons cited above, lacidipine was introduced in our hospital to treat high blood pressure in HSCT children receiving CsA to prevent GVHD. However, no data are available on the magnitude of drug interactions between CCBs and CsA in pediatrics. The aim of this study was to report and quantify pharmacokinetic interactions between

[1]Institut d'Hématologie et d'Oncologie Pédiatrique, Lyon, France
[2]Laboratoire de Biométrie et Biologie Evolutive, Université Lyon 1, Villeurbanne, France

Corresponding Author:
Nathalie Bleyzac, Institut d'Hématologie et d'Oncologie Pédiatrique, 1 Place Joseph Renaut, 69008 Lyon, France.
Email: nathalie.bleyzac@chu-lyon.fr

Table 1. Variations in CsA TBCs to Dose-Normalized CsA Ratio Associated With CCB Treatment.

CCB	TBC/Dose Ratio Before Starting CCBs	TBC/Dose Ratio After 3-7 Days of CCB Therapy	*P* (Wilcoxon)
Nicardipine (n = 17)	43.6 ± 33.4	71.8 ± 45.9	<0.001
Amlodipine (n = 16)	34.3 ± 27.1	58.0 ± 46.4	0.001
Lacidipine (n= 18)	34.3 ± 15.2	36.0 ± 19.0	0.500

Abbreviations: CCB, calcium channel blockers; CsA, cyclosporine; TBC, trough blood concentration.

the CCBs—that is, nicardipine, amlodipine, lacidipine, and CsA.

Methods

Design

This was a retrospective analysis of data from children who received allogeneic stem cell transplantation between 2000 and 2012 in our institution.

Participants and Setting

All patients under CsA who received concomitant CCBs were included. IV nicardipine was used when blood pressure was life threatening, as emergency treatment. The first-used oral CCB was amlodipine. It has been replaced by lacidipine from 2008 to avoid drug-drug interactions mediated by CYP3A4. Initial CCB dosage regimens used were 0.05 mg/kg/h for nicardipine, 0.15 mg/kg/d for amlodipine, and 0.05mg/kg/d for lacidipine. For each CCB, the dose was increased gradually until effective control of hypertension was achieved.

Exclusion criteria were (1) unknown date of CCB introduction, (2) treatment with other known CYP3A4 inhibitors (eg, azole antifungals, macrolide antibiotics) or inducers, and (3) switch from the IV to the oral route for CsA during CCB therapy.

Interventions

Trough blood concentrations (TBCs) of CsA were measured twice weekly during the first month posttransplantation and then once weekly by antibody-conjugated magnetic immunoassay (ACMIA).[15] Blood sampling was always performed on peripheral venous sites to avoid bias caused by contamination of the central catheter in which CsA was administered. CsA dosing regimens were individually adjusted by using a Bayesian approach described elsewhere.[16] CsA trough blood levels at the steady state were available for all patients before CCB introduction. At the time of CCB onset, patients could receive CsA either intravenously or orally. CsA TBCs were measured for all patients within the first week (between day 3 and day 7) after CCBs were started. Slight dose adjustments may have been performed for each patient to control CsA blood concentration over the study period. Target TBC was set at 120 to 150 ng/mL in patients without GVHD and 150 to 200 ng/mL in case of GVHD occurrence, depending on GVHD severity.[13]

Outcome

Because of those individual changes of CsA dose over the study period, we did not examine actual CsA trough concentrations but dose-normalized trough concentrations, expressed by the ratio of CsA TBC (in ng/mL) over CsA daily dose (in mg/kg). Daily doses were expressed per kilogram of actual body weight, which may also have changed a little over the study period for some patients. Although the unit of dose-normalized TBC is 10^{-6} g kg mL^{-1}, these values are reported without units throughout this article for ease of reading. Dose-normalized TBCs were compared before and after the introduction of CCBs using the Wilcoxon signed rank test for matched samples, with statistical significance set at a *P* value of 5%.

The impact of CCBs on therapeutic drug monitoring was assessed by comparing the mean percentage of deviation between measured TBC and individual target TBC values (which were as follows: in patients without GVHD transplanted for malignant and nonmalignant diseases, 120 and 150 ng/mL, respectively; in patients with grade I, II, and III-IV GVHD, 150, 180, and 200 ng/mL, respectively).

Results

Number of Participants

In all, 51 transplanted children (from 2 months to 17 years old) receiving CsA were included in the study. They were concomitantly treated with CCBs as follows: 17 received nicardipine (10 male [M], 7 female [F] patients; age: 4.8 ± 5.7 years), 16 received amlodipine (8 M, 8 F; age = 3.9 ± 4.0 years), and 18 received lacidipine (10 M, 8 F; age = 6.2 ± 4.5 years).

Outcome

Dose-normalized TBCs over the study period are reported in Table 1. The TBC/dose ratio at baseline appears to be higher for nicardipine than for amlodipine or lacidipine,

Table 2. Deviation (Dev) Between Measured CsA TBCs and Target TBC Values Associated With CCB Treatment.

CCB	Dev Before Starting CCBs (%)	Dev After 3 to 7 Days of CCB Therapy (%)	P (Wilcoxon)
Nicardipine (n = 17)	19.8 ± 17.7	58.4 ± 53.1	0.010
Amlodipine (n = 16)	15.5 ± 12.5	46.0 ± 46.2	0.014
Lacidipine (n = 18)	20.8 ± 19.2	25.9 ± 25.8	0.432

Abbreviations: CCB, calcium channel blockers; CsA, cyclosporine; TBC, trough blood concentration.

although the differences were not significant (Kruskal-Wallis, $P = 0.407$). Nevertheless, this could be explained by higher blood pressure (probably related to higher CsA blood concentrations), justifying the use of IV CCB (nicardipine) in the emergency setting. The mean dose-normalized TBCs significantly increased after 3 to 7 days in patients treated with nicardipine and amlodipine but not in those who received lacidipine. The mean percentage of increase in CsA dose-normalized TBC was 86.5%, 74.3%, and 5.1% for nicardipine, amlodipine, and lacidipine, respectively. Intrapatient variability in dose-normalized TBCs over the 3 weeks before introduction of CCB treatment was much lower (4.7 ± 2.6) than the alteration observed after nicardipine or amlodipine introduction. The increase in CsA mean dose-normalized TBC associated with amlodipine was significant irrespective of CsA administration route (IV CsA, n = 9, $P = 0.015$; oral CsA, n = 7, $P = 0.018$). It was 24% higher when CsA was administered orally than intravenously (po CsA: 23 ± 6 and 43 ± 22, respectively, before and after amlodipine; IV CsA: 43 ± 34 and 70 ± 57, respectively, before and after amlodipine). Obviously, the small number of patients in each group makes it difficult to arrive at any conclusion, even though a major involvement of intestinal CYP3A4 inhibition could be suspected. The influence of CsA administration route could not be statistically examined for nicardipine because only 4 patients in this group received oral CsA. Lacidipine did not significantly increase CsA mean dose-normalized TBC in children who received CsA by both the IV ($P = 0.937$) and oral routes ($P = 0.249$).

The magnitude of the drug-drug interaction in each group was not correlated with age (Spearman's rank correlation: nicardipine, $P = 0.948$; amlodipine, $P = 0.130$; lacidipine, $P = 0.522$).

Deviations of CsA TBC from target values are given in Table 2. Only lacidipine had no impact on the mean deviation magnitude and, therefore, did not increase the number of patients out of the target range. In the majority of patients with CSA concentrations within the therapeutic range before CCB administration, time to achieve target CSA concentrations again after CCB introduction exceeded 1 week.

Limitations

As specified above, this study was retrospective. Treatment allocation was not randomized. The repartition of patients between groups depended on historical changes in practices.

Conclusions

CCBs, especially those from the dihydropyridine class, are widely used to treat high blood pressure induced by CsA. Most of them, especially those authorized in children, are inhibitors of CYP3A4, which is a key pathway of CsA metabolism. They are also possible inhibitors of P-glycoprotein. As a result, coadministration of CCB with CsA may lead to an increase in CsA blood concentrations. This change in CsA exposure can be managed by appropriate therapeutic drug monitoring and dosage adjustment in clinical practice. However, the time necessary to reach target blood concentrations may be longer, compromising the efficiency of CsA treatment. Indeed, the exposure to target CsA blood concentration is essential in order to obtain mild GVHD in leukemia patients (graft-versus-leukemia effect) and no GVHD in others.[17-20] Moreover, CCB-induced decrease in CsA metabolism may alter the contribution of active metabolites in the immunosuppressive effect of CsA and possibly change the pharmacological profile of the drug.[21] Thus, treating hypertension with a drug that increases CsA blood levels may consequently enhance hypertension and would thus not be suitable.[1] The identification of the safest CCB regarding potential drug-drug interactions with CsA is desirable in HSCT children.

This report examined the influence of 3 CCBs on CsA exposure in children from 2 months to 17 years old. Although drug-drug interactions between CsA and some calcium antagonists are well documented in adults, information regarding children is poor. Extrapolation of drug interaction data from adults to children may not be valid because of particular susceptibility of children to drug-drug interactions caused by ontogeny of metabolic pathways and drug transporters.[22,23]

In this study, a significant increase in CsA dose-normalized TBC was observed in children who were coadministered amlodipine and nicardipine, whereas no significant change in dose-normalized CsA TBCs was observed in children who received lacidipine.

Published data on amlodipine-CsA drug interaction are conflicting. Some studies have suggested no significant interaction between amlodipine and CsA.[24-27] However,

those study conclusions are undermined by important flaws in data collection and analysis such as (1) sparse timing of CsA monitoring around amlodipine introduction, (2) lack of matched samples for all patients, and (3) pooled data analysis. In a well-designed study, Pesavento et al[28] showed a 40% increase in CsA blood concentrations in renal transplant adults treated by amlodipine during several weeks, with a return to initial values after amlodipine withdrawal. These results have been confirmed in a recent study.[29] In our study, the average increase in CsA exposure associated with amlodipine introduction was 74%, but large interpatient variability was observed in this effect. Indeed, one patient had no change of dose-normalized TBC, 6 patients showed an increase of less than 50%, and 5 patients showed an increase of more than 100%.

The interaction between CsA and nicardipine appears to be less controversial in the literature, with an average increase in CsA blood concentrations of 80% associated with this CCB.[30-32] The latter is in agreement with our findings. Effectively, nicardipine appears to have the strongest CYP3A4 inhibition potency among CCBs.[12] The large magnitude of blood concentration increase observed with nicardipine may also be the result of P-gp inhibition. Indeed, nicardipine is one of the strongest P-gp inhibitors among CCBs.[33]

Scarce data are available regarding the interaction between lacidipine and CsA. Two studies that included 10 and 59 renal transplant adults did not find any significant influence of lacidipine on CsA blood concentrations.[34,35] However, in both studies, a pooled analysis of CsA blood levels before and after lacidipine introduction was performed, which undermines the conclusion. Our results suggest the lack of pharmacokinetic interaction between lacidipine and CsA. This is in agreement with in vitro results from Xia et al[13] who measured a relatively high CYP3A4 inhibition constant (Ki) for lacidipine, suggesting little or no inhibition potency.

This analysis has several limitations that should be considered, including (1) the uncontrolled, retrospective design; (2) lack of patients' full pharmacokinetic profile of CsA; and (3) the limited sample size. Interaction of CCBs with CYP3A4 might not be the only mechanism of interaction. But the design of the study did not allow us to determine the quantitative involvement of transporter inhibition by CCBs.

Furthermore, as well as being a substrate, CsA is also an inhibitor of both CYP3A4 and transporters such as P-glycoprotein and OATP.[36] A potential interaction of CsA with CCBs could be expected, as already observed.[37] However, the magnitude of the interaction on transporters depends on the subsequent concentration reached in the gut wall, the inhibition potency toward the different transporters, and the mechanism of inhibition.[38] So the impact of inhibition of CCB transport by CsA on their pharmacokinetics might be different for each CCB and could even be minor compared to CYP3A4 inhibition.[39] These issues were not studied in this work.

To our knowledge, this is the first analysis of the influence of several CCBs on CsA exposure in children. Our results suggest that lacidipine may be the best option among CCBs to treat high blood pressure related to CsA in children because of the lack of significant drug interaction with CsA. If nicardipine or amlodipine are chosen or are the only options available, our findings indicate that increased CsA monitoring is required. In contrast, the absence of drug interaction between lacidipine and CsA may facilitate this monitoring and help keep individual patients' exposure within the target range.

Declaration of Conflicting Interests

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References

1. Robert N, Wong GW, Wright JM. Effect of cyclosporine on blood pressure. *Cochrane Database Syst Rev*. 2010;(20):1-50 doi:10.1002/14651858.CD007893.
2. Hoorn EJ, Walsh SB, McCormick JA, Zietse R, Unwin RJ, Ellison DH. Pathogenesis of calcineurin inhibitor–induced hypertension. *J Nephrol*. 2012;25:269-275 doi:10.5301/jn.5000174.
3. Rodicio JL. Calcium antagonists and renal protection from cyclosporine nephrotoxicity: long-term trial in renal transplantation patients. *J Cardiovasc Pharmacol*. 2000;35:S7-S11.
4. Luft FC. How calcineurin inhibitors cause hypertension. *Nephrol Dial Transplant*. 2012;27:473-475. doi:10.1093/ndt/gfr679.
5. Pfeilschifter J, Rüegg UT. Cyclosporin A augments angiotensin II-stimulated rise in intracellular free calcium in vascular smooth muscle cells. *Biochem J*. 1987;248:883-887.
6. van der Schaaf MR, Hené RJ, Floor M, Blankestijn PJ, Koomans HA. Hypertension after renal transplantation: calcium channel or converting enzyme blockade? *Hypertension*. 1995;25:77-81.
7. Khattak S, Rogan JW, Saunders EF, Theis JG, Arbus GS, Koren G. Efficacy of amlodipine in pediatric bone marrow transplant patients. *Clin Pediatr*. 1998;37:31-35.
8. Rogan JW, Lyszkiewicz DA, Blowey D, Khattak S, Arbus GS, Koren G. A randomized prospective crossover trial of amlodipine in pediatric hypertension. *Pediatr Nephrol*. 2000;14:1083-1087.
9. Flynn JT. Efficacy and safety of prolonged amlodipine treatment in hypertensive children. *Pediatr Nephrol*. 2005;20:631-635.

10. Andersen J, Groshong T, Tobias JD. Preliminary experience with amlodipine in the pediatric population. *Am J Ther*. 2006;13:198-204.
11. Guengerich FP, Brian WR, Iwasaki M, Sari MA, Baarnhielm C, Berntsson P. Oxidation of dihydropyridine calcium channel blockers and analogues by human liver cytochrome P-450 IIIA4. *J Med Chem*. 1991;34:1338-1344.
12. Katoh M, Nakajima M, Shimada N, Yamazaki H, Yokoi T. Inhibition of human cytochrome P450 enzymes by 1,4-dihydropyridine calcium antagonists: prediction of in vivo drug-drug interactions. *Eur J Clin Pharmacol*. 2000;55:843-852.
13. Xia Z, Wang M, Zou S, Chen R. Different effects of dihydropyridine calcium channel antagonists on CYP3A4 enzyme of human liver microsomes. *Eur J Drug Metab Pharmacokinet*. 2012;37:211-216. doi:10.1007/s13318-011-0076-3.
14. Hebert MF. Contributions of hepatic and intestinal metabolism and P-glycoprotein to cyclosporine and tacrolimus oral drug delivery. *Adv Drug Deliv Rev*. 1997;27:201-214.
15. Huet E, Morand K, Blanchet B, Astier A, Hulin A. Evaluation of the new heterogeneous ACMIA immunoassay for the determination of whole-blood cyclosporine concentrations in bone marrow, kidney, heart, and liver transplant recipients. *Transplant Proc*. 2004;36:1317-1320.
16. Bleyzac N. The use of pharmacokinetic models in paediatric onco-haematology: effects on clinical outcome through the examples of busulfan and cyclosporine. *Fundam Clin Pharmacol*. 2008;22:605-608. doi:10.1111/j.1472-8206.2008.00652.x.
17. Martin P, Bleyzac N, Souillet G, et al. Relationship between cyclosporine trough blood concentrations and severity of acute graft-versus-host-disease after paediatric stem cell transplantation from matched-sibling or unrelated donors. *Bone Marrow Transplant*. 2003;32:777-784.
18. Martin P, Bleyzac N, Souillet G, et al. Clinical and pharmacological risk factors for acute graft-versus-host disease after paediatric stem cell transplantation from matched-sibling or unrelated donors. *Bone Marrow Trans-plant*. 2003;32:881-887.
19. Willemze AJ, Press RR, Lankester AC, Egeler RM, den Hartigh J, Vossen JM. CsA exposure is associated with acute GVHD and relapse in children after SCT. *Bone Marrow Transplant*. 2010;45:1056-1061. doi:10.1038/bmt.2009.299.
20. Gérard C, Bleyzac N, Girard P, Freyer G, Bertrand Y, Tod M. Links between cyclosporin exposure in tissues and graft-versus-host disease in pediatric bone marrow transplantation: analysis by a PBPK model. *Pharm Res*. 2011;28:531-539. doi:10.1007/s11095-010-0299-z.
21. Ozbay A, Karamperis N, Jørgensen KA. A review of the immunosuppressive activity of cyclosporine metabolites: new insights into an old issue. *Curr Clin Pharmacol*. 2007;2:244-248.
22. Salem F, Rostami-Hodjegan A, Johnson TN. Do children have the same vulnerability to metabolic drug–drug interactions as adults? A critical analysis of the literature. *J Clin Pharmacol*. 2013;53:559-566.
23. Salem F, Johnson TN, Barter ZE, Leeder JS, Rostami-Hodjegan A. Age related changes in fractional elimination pathways for drugs: assessing the impact of variable ontogeny on metabolic drug-drug interactions. *J Clin Phar-macol*. 2013;53:857-865. doi:10.1002/jcph.100.
24. Toupance O, Lavaud S, Canivet E, Bernaud C, Hotton JM, Chanard J. Antihypertensive effect of amlodipine and lack of interference with cyclosporine metabolism in renal transplant recipients. *Hypertension*. 1994;24:297-300.
25. Pfammatter JP, Clericetti-Affolter C, Truttmann AC, Busch K, Laux-End R, Bianchetti MG. Amlodipine once-daily in systemic hypertension. *Eur J Pediatr*. 1998;157:618-621.
26. von Vigier RO, Franscini LM, Bianda ND, et al. Antihypertensive efficacy of amlodipine in children with chronic kidney diseases. *J Hum Hypertens*. 2001;15:387-391.
27. Chanard J, Toupance O, Lavaud S, Hurault de Ligny B, Bernaud C, Moulin B.Amlodipine reduces cyclosporin-induced hyperuricaemia in hypertensive renal transplant recipients. *Nephrol Dial Transplant*. 2003;18:2147-2153.
28. Pesavento TE, Jones PA, Julian BA, Curtis JJ. Amlodipine increases cyclosporine levels in hypertensive renal transplant patients. *J Am Soc Nephrol*. 1996;7:831-835.
29. Cai J, Huang Z, Yang G, et al. Comparing antihypertensive effect and plasma cyclosporin concentration between amlodipine and valsartan regimens in hypertensive renal transplant patients receiving ciclosporin therapy. *Am J Cardiovasc Drugs*. 2011;11:401-409. doi:10.2165/11593800-000000000-00000.
30. Todd P, Garioch JJ, Rademaker M, Thomson J. Nicardipine interacts with cyclosporin. *Br J Dermatol*. 1989;121:820.
31. Bagnis C, Deray G. Calcium inhibitors in the management of hypertensive patients on cyclosporine. *Arch Mal Coeur Vaiss*. 1998;91:411-414.
32. Guan D, Wang R, Lu J, Wang M, Xu C. Effects of nicardipine on blood cyclosporine levels in renal transplant patients. *Transplant Proc*. 1996;28:1311-1312.
33. Katoh M, Nakajima M, Yamasaki H, Yokoi T. Inhibitory potencies of 1,4 dihydropyridine calcium antagonists to P-glycoprotein-mediated transport: comparison with the effects on CYP3A4. *Pharm Res*. 2000;10:1189-1197.
34. Ruggenenti P, Perico N, Mosconi L, et al. Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hypoperfusion. *Kidney Int*. 1993;43:706-711.
35. Kuypers DR, Neumayer HH, Fritsche L, et al. Calcium channel blockade and preservation of renal graft function in cyclosporine-treated recipients: a prospective randomized placebo-controlled 2-year study. *Transplantation*. 2004;78:1204-1211.
36. Gertz M, Cartwright CM, Hobbs MJ, et al. Cyclosporine inhibition of hepatic and intestinal CYP3A4, uptake and efflux transporters: application of PBPK modeling in the assessment of drug-drug interaction potential. *Pharm Res*. 2013;30:761-780.
37. Madsen JK, Jensen JD, Jensen LW, Pedersen EB. Pharmacokinetic interaction between cyclosporine and the dihydropyridine calcium antagonist felodipine. *Eur J Clin Pharmacol*. 1996;50:203-208.
38. Gertz M, Houston JB, Galetin A. Physiologically based pharmacokinetic modeling of intestinal first-pass metabolism of CYP3A substrates with high intestinal extraction. *Drug Metab Dispos*. 2011;39:1633-1642.
39. Dorababu M, Nishimura A, Prabha T, et al. Effect of cyclosporine on drug transport and pharmacokinetics of nifedipine. *Biomed Pharmacother*. 2009;63:697-702.