

Two-hour Postdose Level of Cyclosporine Monitoring of Solid Organ Transplant Patients

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Dear Editor,

I read with great interest the article, "Cyclosporine level at the second hour in pediatric hematopoietic stem cell transplant patients" by Balci and associates.¹ This retrospective study focused its message on whether the second hour (C2) of blood level monitoring in pediatric hematopoietic stem cell transplant recipients should be done routinely. They concluded that in pediatric hematopoietic stem cell transplant patients, measurement of C2 levels as a standard practice did not offer any advantage over cyclosporine trough level (C0) monitoring; however, C2 blood level monitoring could be useful in select recipients with an increased risk of nephrotoxicity, or in states where a better estimation of gastrointestinal absorption is required.

Although cyclosporine is used widely after a solid organ transplant over the long term, there is still no firm consensus on the best way to monitor cyclosporine in the blood.² A narrow therapeutic blood level of cyclosporine has led to monitoring its blood concentration. Cyclosporine pharmacokinetics has interindividual and intraindividual variability, and pediatric recipients require larger dosages than adults owing to variations in biological maturation.³ Contributing factors in pediatric recipients is the variation of cyclosporine bioavailability through the intestinal length, metabolism in the gut, type of organ transplant, and transplant duration.⁴ In addition, trough levels of cyclosporine are significantly lower in the evening (C12) than in the morning (C0), which indicates that there is circadian variation in metabolism of this drug.⁵

I agree that C2 blood levels are significantly correlated with blood creatinine values, as seen in this study,¹ as well as in our previous study of 236 pediatric renal transplant recipients.⁶ However, Cole and associates reported no correlation between C2 and serum creatinine.⁷

Although Balci and associates¹ revealed a significantly lower level of C2 in younger patients, no significant correlation was seen between C2 blood level and age of pediatric renal transplant recipients.⁷ Despite the fact that systemic clearance is relatively higher in children than it is in adults, there is no difference in volume of distribution of cyclosporine between pediatric and adult transplant recipients.^{4, 8} Balci and associates¹ found no statistically significant relation between sex and C0 and C2 levels, although C0 levels of the girls (170 ng/mL) were higher than those of the boys (146 ng/mL); however, we showed that C0 level was higher in boys than in girls ($P = .000$), but this difference was not seen for the C2 level among the sexes ($P = .3$).⁷ P-glycoprotein, a transmembrane transporter, is present in the endothelium of several tissues, such as the brain, lung, and kidney. It transports immunosuppressant drugs such as cyclosporine, tacrolimus, and sirolimus. In women, P-glycoprotein is expressed less so than it is in men. This could explain the sex-related differences in the pharmacokinetics of immunosuppressant drugs.⁹

I agree that C2 blood level assay has priority over cyclosporine trough (C0) level monitoring; however, despite the general belief that it is the most-sensitive marker for the area under the curve of the drug, and it has been planned as a more-convenient method for pharmacokinetic monitoring than C0 assay,^{10, 11} in clinical practice, therapeutic drug monitoring of cyclosporine with C0 blood levels continues to be used routinely, mainly because it is easier. In fact, C2 blood level measurement requires a second blood

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sample; thus, 2 blood samples must be taken from each patient, and this can cause noncompliance problems, especially owing to interrupted work time during the day. On the other hand, precise timing of blood samples for C₂ values is crucial. Consensus guidelines suggest there is a 10-minute “window of opportunity” before and after the 2-hour point when samples should be taken.¹²

References

- Balci YI, Tavil B, Karabulut E, et al. Cyclosporine level at the second hour in pediatric hematopoietic stem cell transplant patients. *Exp Clin Transplant*. 2011;9(5):329-335.
- Rostami Z, Einollahi B. Cyclosporine monitoring in organ transplantation: Do we need a new concept? *Nephro-Urol Mon*. 2011;3(2):97-98.
- Tönshoff B, David-Neto E, Ettenger R, et al. Pediatric aspects of therapeutic drug monitoring of mycophenolic acid in renal transplantation. *Transplant Rev (Orlando)*. 2011;25(2):78-89.
- Cooney GF, Habucky K, Hoppu K. Cyclosporin pharmacokinetics in paediatric transplant recipients. *Clin Pharmacokinet*. 1997;32(6):481-495.
- Federico S, Carrano R, Capone D, Gentile A, Palmiero G, Basile V. Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet*. 2006;45(2):169-175.
- Beiraghdar F, Rostami Z, Einollahi B. Cyclosporine through and 2 hour post dose monitoring and its contributing factors among pediatric kidney recipients. *Nephro-Urol Mon*. 2011;3:223-227.
- Cole E, Maham N, Cardella C, et al. Clinical benefits of neoral C₂ monitoring in the long-term management of renal transplant recipients. *Transplantation*. 2003;75(12):2086-2090.
- Halloran PF, Helms LM, Kung L, Noujaim J. The temporal profile of calcineurin inhibition by cyclosporine in vivo. *Transplantation*. 1999;68(9):1356-1361.
- Pieri M, Miraglia N, Polichetti G, Tarantino G, Acampora A, Capone D. Analytical and pharmacological aspects of therapeutic drug monitoring of mTOR inhibitors. *Curr Drug Metab*. 2011;12(3):253-267.
- Gaspari F, Caruso R, Cattaneo D, Perico N, Remuzzi G. Optimization of cyclosporine therapy in the Neoral era: abbreviated AUC, single blood sampling? *Transplant Proc*. 2001;33(7-8):3117-3119.
- Pape L, Lehnhardt A, Latta K, Ehrlich JH, Offner G. Cyclosporin A monitoring by 2-h levels: preliminary target levels in stable pediatric kidney transplant recipients. *Clin Transplant*. 2003;17(6):546-548.
- Knight SR, Morris PJ. The clinical benefits of cyclosporine C₂-level monitoring: a systematic review. *Transplantation*. 2007;83(12):1525-1535.