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신이식 초기에 MDR1, CYP3A4, CYP3A5 유전자 다형태가 사이클로스포린의 집단 약동학적 지표에 미치는 영향에 관한 연구

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The Effects of MDR1, CYP3A4, and CYP3A5 Gene Polymorphisms on the Population Pharmacokinetics of Cyclosporine in Non-steady-state Renal Transplant Recipients

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Background : Many studies have investigated the relationships between the pharmacokinetics (PK) of cyclosporine (CsA) and genetic polymorphisms of MDR1, CYP3A4, and CYP3A5 in stable-state renal transplant recipients. However, information is lacking on the corresponding relationships in the early, non-steady-state post-transplantation period.

Objective : The main objectives were elucidation of the changes in the PK parameters of CsA in the first 2-3 days post-transplantation, and the influences of MDR1, CYP3A4, and CYP3A5 polymorphisms. We also estimated the optimal correlating single time-point concentration with AUC0-12, which may be useful as a target drug concentration for monitoring during the early post-transplantation period.

Methods : The PK of CsA was studied in 69 renal transplant recipients on Day 2 and Day 3 after transplantation using nonlinear mixed-effects modeling (NONMEM). The patients were genotyped for the MDR1 C3435T, CYP3A4×1B, and CYP3A5×3 single nucleotide polymorphisms (SNPs). Correlation analysis was performed to identify the single time-point that best correlated with AUC0-12.

Results : The PK model showed significant increases in the absorption rate constant (Ka) and bioavailability on Day 3, as compared to Day 2. There were no significant daily changes in the volume of distribution, systemic clearance, and absorption lag time. Only the MDR1 C3435T genotype affected an increase in Ka. Homozygous wild-type individuals (N=24) showed a more pronounced increase in Ka between Day 2 and Day 3 than mutant-allele carriers (N=45) (p=0.0065). The single time-point best correlated with AUC0-12 occurred 8 h after the administration of CsA (C8) in both groups on Day 2 and in the mutant-allele carriers on Day 3. C6 was the optimal single time-point in patients with wild-type MDR1 on Day 3.

Conclusion : In the non-steady state immediately after renal transplantation, the absorption and bioavailability of CsA increased more prominently on Day 3 than on Day 2, and the increase in absorption was greater in MDR1 wild-type patients. Also, C0 or C2 monitoring to adjust the dosage of CsA may result in inadequate immunosuppression during the early post-transplantation period.

Key Words : 신이식, 사이클로스포린, 유전자 다형태
Transplantation, Cyclosporine, Polymorphisms