한국임상약학회지 제21권 제4호
Kor. J. Clin. Pharm., Vol. 21, No. 4. 2011

조혈모세포 이식환자에서 항생제 투여에 의한 cyclosporine의 혈중농도변화

송헌정[1] · 유옥리[1] · 최유리[1] · 방준석[1#] · 나현오[2#]
[1]가톨릭대학교 서울성모병원 약제부, [2]가톨릭대학교 의과대학 약리학교실
(2011년 8월 19일 접수 · 2011년 11월 16일 수정 · 2011년 11월 18일 승인)

Alterations of Cyclosporine Concentrations by Antibiotics in Patients with Hematopoietic Stem Cell Transplantation

Hun Jung Song,[1] Liu Yu Li,[1] Yuri Choi,[1] Joon Seok Bang,[1] and Hyen Oh La[2]
[1]*Department of Pharmacy, Seoul St. Mary's Hospital, The Catholic University of Korea*
[2]*Department of Pharmacology, College of Medicine, The Catholic University of Korea*
505, Banpo-dong, Seocho-gu, Seoul, 137-701, Korea

(Received August 19, 2011 · Revised November 16, 2011 · Accepted November 18, 2011)

조혈모세포이식술(또는 HSCT)을 받은 환자에게는 이식관련 부작용의 예방 또는 치료를 위해 면역억제 약물이 투여되는데, 그 중 하나인 cyclosporine은 therapeutic index가 작고 다양한 요인에 의해 혈중농도가 변화되므로 사용시에는 세심한 관찰과 조절이 필요하다. 특히 HSCT 환자에서 발생하는 호중구 감소성 발열(또는 NPF)의 치료목적으로 투여하는 항생제에 의하여 cyclosporine의 혈중농도가 변화될 수 있고, 또 임상적 경과에 따라 항생제 처방이 중도에 변경되는 경우도 빈번하지만, 실제로 항생제 처방의 중간변경에 의한 cyclosporine의 혈중농도 변화양상을 연구한 결과는 많지 않다. 이에, 과거 2년 동안 한 상급종합병원에서 HSCT후 cyclosporine을 투여 받았던 환자 중에서 통상적인 NPF 치료용 항생제인 ciprofloxacin을 투여하다가 치료성과를 높이기 위하여 cefepime으로 대체 투여했던 환자들의 의무기록을 후향적으로 분석하였다. 1차 선택약인 ciprofloxacin에서 항생제를 변경했을 때 cyclosporine의 혈중농도가 유의성 있게 증가했는데, 이는 ciprofloxacin 보다 cefepime이 간에서 cyclosporine을 분해시키는 효소생성을 억제시켰기 때문일 것으로 예측되며, HSCT 환자에서 NPF 치료용 항생제를 ciprofloxacin에서 cefepime으로 변경 시에는 병용중인 cyclosporine 유지용량을 약 13% 감량하는 것이 cyclosporine의 효과는 유지하면서 부작용의 발생위험을 감소시키는 데 유용한 방안이 될 것으로 사료된다.

□ Key words - HSCT, cyclosporine, neutropenic fever, ciprofloxacin, cefepime, drug-drug interaction

Along with introducing more immune-suppressive agents into clinical settings to prevent graft-versus-host disease (GVHD) in patients with hematopoietic stem cell transplant (HSCT), the intricacy of drug-drug interactions (DDIs) has increased and become growing challenges to clinicians. Moreover, clinically relevant DDIs among immune-suppressants have also become complex, therefore, it requires identification and monitoring.[1,2)]

Cyclosporine (CS), a calcineurine inhibitor, is one of the frequently adopted immune-suppressants. However, it has a small therapeutic index, fluctuate blood-levels, and affects pharmacokinetic alterations. Hence, therapeutic drug monitoring (TDM) of CS is a crucial process to individualize the drug in HSCT-patients.[3,4)] And a medication, which is metabolized by CYP3A4 in hepatic system, or either inducing or inhibiting CYP enzymes, is administered concurrently with CS, blood-levels of CS will be easily affected.[5-7)] According to a clinical standard, CS is infused intravenously one day before HSCT operation and if neutropenic fever (NPF) occurs, antibiotics are applied such as aminoglycosides,

Correspondence to : Joon Seok Bang
Department of Pharmacy, Seoul St. Mary's Hospital, The Catholic University of Korea
Tel: +82-2-2258-2571, Fax: +82-2-2258-2526
E-mail: bjs0191@hotmail.com
Hyen Oh La
Department of Pharmacology, College of Medicine, The Catholic University of Korea
Tel: +82-2-2258-2520, Fax: +82-2-2258-2526
E-mail: hola@cmcnu.or.kr

cephalosporins, glycopeptides, or quinolones for the prophylaxis against many pathologic events derived from the delayed-engraftment of stem cells.[8] Then, NPF is subsided in consequence of antimicrobial treatment, CS could be resumed.[9] When absolute neutrophil count (ANC) value is reached greater than 1000 mm^3, administration route of CS could be converted from intravenous to oral. However, studies reported that antimicrobials such as azoles, macrolides, or cephalosporins could induce DDIs and eventually increase the blood concentrations of CS in HSCT-patients.[10-12]

Cefepime, the 4th generation cephalosporin, is widely adopted recently against NPF in the HSCT fields.[13-17] However, few studies were conducted to evaluate the DDI between CS and cefepime. So, for maintaining the efficacy of CS, the understanding of confounding factors that affect its blood-concentration of CS is essential. Therefore, this study was performed in order to elucidate the alterations of blood concentration of CS with co-administering of antibiotics in HSCT-patients.

MATERIALS AND METHODS

Subject Selection

Patients who are satisfying the following criteria were chosen as the sample subjects in a university hospital: between January 2007 and December 2008; those who received HSCT with a history of CS by intravenously for preventing GVHD and attained a steady-state blood concentration; those who converted antibiotics from ciprofloxacin to cefepime when NPF occurred during their treatment. However, those who had previous HSCT with additional transplantation; and those who prescribed immune-suppressing agents except cyclosporine were excluded in the study. In adherence with the intra-organizational guideline, 500 mg/day CS were applied for the immune-compromised patients to prevent any kind of infection, and co-administered 6000 mg/day cefepime to relieve NPF.[15-17]

Data Collection

Data were collected retrospectively via patient's monitoring profiles (PMPs) and institutional electronic medical records among 18-year-old and older patients who met the criteria. The data for quantitative analyses were as follows: basic demographic and pathophysiologic properties including age, gender, height, weight, BMI, disease, and HSCT-type; the levels of hepatic function indicators such as total bilirubin (T-bil), aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Study protocol was completely reviewed by the Institutional Review Board for clinical trial study and was found to obey all regulations and guidelines of the Korea Good Clinical Practice (KGCP), International Conference on Harmonization Good Clinical Practice (ICH-GCP), and specified bioethical regulations (Assignment No: KC09RISI0284; Sep. 21, 2009).

Dosage and Blood Concentration Ratio of Cyclosporine

Although the blood concentrations of CS has reached the steady-state (C_{ss}) that were decided amount or mean effective dosage, when a drug is used concurrently the next dose of CS should be re-adjusted. Therefore, in order to settle the dosages and blood-levels, we used a standard index or a ratio value of blood-concentration at the C_{ss} over daily amount of dosing. Using the ratio, we analyzed the pharmacokinetic alterations comparing to the values of the hepatic indicators in each patient (Equation 1). Only the concentration obtained at C_{ss} were analyzed. The target range of blood-concentration was 200~300 ng/mL.

$$\text{Ratio} = \frac{[\text{Concentration of cyclosporine (ng/mL)}]}{[\text{Dosing amount of cyclosporine (mg/day/kg)}]} \quad (1)$$

Data Analysis

The obtained data were undergone statistical analyses using SAS program (Ver. 9.1). Both the confounding factors in demographic or pathophysiological aspects and the relationship of variability on liver function were examined using the extent of CS blood-concentration by paired t-test. In addition, variability of liver function was examined by the same method. It was considered statistically significant when *p*-value was less than 0.05.

Table 1. Study population (n=32)

Characteristics		Number of subject (%)
Age (year)	10 ~ 19	3 (9.4)
	20 ~ 29	7 (21.9)
	30 ~ 39	11 (34.4)
	40 ~ 49	5 (15.6)
	50 ~ 59	4 (12.5)
	60 ~ 69	2 (6.0)
Gender	Male	19 (59.4)
	Female	13 (40.6)
BMI (kg/m^2)*	< 18.5 (below normal)	2 (6.3)
	18.5 ~ 23.0 (normal)	15 (46.9)
	23.0 ~ 25.0 (over weight)	8 (25.0)
	25.0 ~ 30.0 (obese)	6 (18.7)
	≥ 31 (seriously obese)	1 (3.1)
Diagnosed disease name of the HSCT patients	Acute myeloid leukemia	15 (46.9)
	Acute lymphocytic leukemia	10 (31.3)
	Severe aplastic anemia	4 (12.5)
	Myelodysplastic syndrome	2 (6.2)
	Chronic myeloid leukemia	1 (3.1)

*BMI (body mass index)

An expert biostatistician participated to minimize experimental biases.

RESULTS

Study Subject

The number of patients who received CS intravenously during the study period was 96, and with exclusion criteria, the selected patients were 32 (33.3%). Mainly, 11 patients (34.3%) were within 30~39 range, and the male (19 patients, 59.4%) exceeded female subject (13 patients, 40.6%). In terms of body weight, there was about equal number of patients with normal or overweight, and underweight plus obese person which counted for 9.4% of the sample group was 3 and 1, respectively. The set of most frequently diagnosed disease (78.2%) was acute myeloid leukemia and acute lymphocytic leukemia (Table 1).

Dosage and Concentration Ratio of Cyclosporine

When the blood-levels reached C_{ss}, both dosage amount and average blood-concentration of CS were as follows: while ciprofloxacin applied simultaneously, the values measured on 7.8-day-elapsed after CS-infusion was considered as C_{ss} (variation range 3~18 days); the mean effective dose was 147 mg/day (90~246); and the mean blood-concentration was 301.9 ng/mL (146.9~534.4). On the other hand, cefepime applied, the values on 13.2 days after starting CS was defined as C_{ss} (5~18); the effective dose of CS was 123 mg/day (80~200); and the mean blood-concentration was 332.9 ng/mL (169.3~473.2).

Table 2. Variation of hepatic enzyme levels in the study subjects after administration of antibiotics

Antibiotics	T-bil (mg/dL)	AST (U/L)	ALT (U/L)
Ciprofloxacin	1.2±0.6	23.4±16.7	54.0±48.1
Cefepime	1.3±0.7	19.2±13.3	32.3±33.4

T-bil (Total Bilirubin); AST (Aspartate Aminotransferase); ALT (Alanine Aminotransferase); and all data shown as mean±SD

Variations in the Blood Concentration of Cyclosporine

The ratio of blood concentration over dosing amount of CS (Eq. 1) increased with statistical significance followed by co-administration of ciprofloxacin or cefepime (p=0.0261). In particular, the average of ratio was 143.7 when ciprofloxacin applied, compared to 159.6 when cefepime applied. By and large, the ratio of CS were greater when cefepime than ciprofloxin.

Alterations in Hepatic Functions by Antibiotics

When cefepime was administered instead of ciprofloxacin, 3 types of indicators in hepatic system were observed as follows: both antibiotics have affected on liver function and the changes in ALT-level were greater than AST (Table 2). The number of patient whose T-bil increased was 14 (43.8%), and T-bil decreased was 18 (56.2%) (p=0.572); whose AST-level increased was 13 (40.6%), but the decreased was 19 (59.4%) (p=0.268); whose ALT-level increased was 8 (25%), but the decreased was 24 (75%) (p=0.043). Although statistical significance was not confirmed, there were a greater number of patients those T-bil and

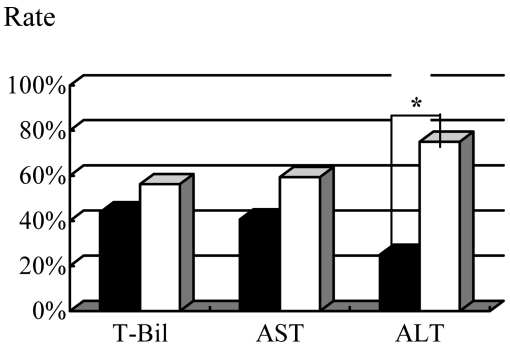

Fig. 1. Rate of changes in hepatic functions after converting antibiotics in patients with cyclosporine: increased (■) or decreased (□) case of the blood concentrations in study subjects; *p<0.05

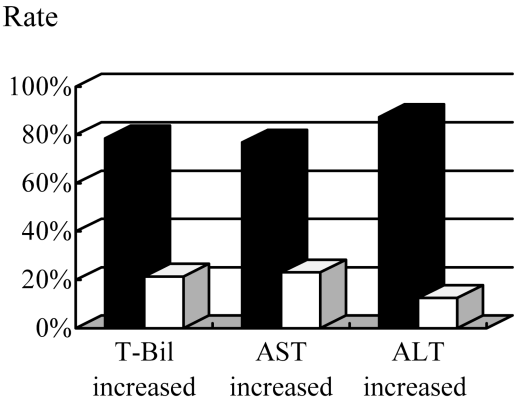

Fig. 2. Variation of the blood levels of cyclosporine in each group of increased hepatic enzymes: increased (■) or decreased (□) cases in the blood concentrations of cyclosporine.

AST-level increased than the decreased, and those decreased ALT demonstrated statistical significance (Fig. 1).

Drug-drug Interaction between Cyclosporine and Cefepime

After co-administration of cefepime, the relationship between the reduction of hepatic function and the blood-concentration of CS in the study patients was as follows: First, out of 14 patients (43.8%) whose T-bil level increased, the number of patients whose blood-concentration of CS increased was 11 (78.6%) and the decreased was 3 (21.4%) (p=0.2656); Second, out of 13 patients (40.6%) whose AST-level increased, the number of patients whose concentration of CS increased was 10 (76.9%) and the decreased was 3 (27.3%) (p=0.4501); Third, out of 8 patients (25%) whose ALT-level increased, the number of patients whose concentration of CS increased was 7 (87.5%) and the decreased was 1 (12.5%) (p=0.2093) (Fig. 2).

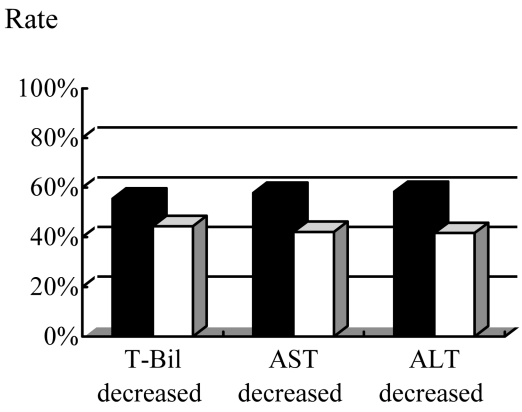

Fig. 3. Variation of the blood levels of cyclosporine in each group of decreased hepatic enzymes: increased (■) or decreased (□) cases in the blood concentrations of cyclosporine.

To the contrary, in patients whose hepatic enzyme levels are decreased after cefepime administration, the alteration in the blood-concentration of CS was as follows: out of 18 patients (56.2%), the number of patients whose CS blood-level increased was 10 (55.6%), and the decreased was 8 (44.4%); out of 19 patients (59.4%) whose AST-level decreased, the number of patients whose CS concentration increased was 11 (57.9%), and the decreased was 8 (42.1%); out of 24 patients (75%) whose ALT-level decreased, the number of patients whose CS blood-concentration increased was 14 (58.3%), and the decreased was 10 (41.7%) (Fig. 3).

According to our estimation, 300 ng/mL is considered as optimal blood-concentration of CS in patients with HSCT followed by cefepime. Furthermore, to attain this value, we proposed approximately 13% dosage-reduction of CS is useful in clinical practices (Table 3).

Table 3. Clinical references of cyclosporine to secure therapeutic outcomes after cefepime administration in patients with lowered hepatic function (target concentration is 300 ng/mL)

Number of patients (n)	C_{ss} after cefepime (ng/mL)	$Dose_{ss}$ after cefepime[a] (mg/day)	Adjusted dose to maintain target concentration[b] (mg/day)	Percentage of dose reduction needed[c] (%)
12	351.8±47.9	147.1±32.4	121.3±28.6	13.4±10.6

C_{ss} (blood concentration of cyclosporine in steady-state); $Dose_{ss}$ (dosing amount of cyclosporine in steady-state); any dosing amount of cyclosporine was derived proportionate to patient's body weight; c = [(a-b)/a] x100; and all data shown as mean±SD

DISCUSSION

Multiple drug therapy or polypharmacy is a common therapeutic practice, particularly in patients with HSCT, and as a results, many DDIs involving metabolic inhibition are being reported.[18,19] Usually, in order to yield effectiveness and to decrease possible adverse events in immuosuppressive pharmacotherapy, the adequate range of blood-concentration needs to be maintained according to elaborate TDM activities. However, assessment of immunosuppressive drug interactions is no longer a fixed, concentration-controlled process; it involves knowledge of drug metabolites, complex drug disposition mechanisms, predictive analytical models, clinical covariates, donor's organ properties and time-related changes in the patient, and grafts characteristics, and so on.[6,10]

In this research, we found the influencing factors that assure appropriate clinical monitoring of CS in HSCT patient is outlined below: [1] Followed by HSCT, immunosuppressants and antibiotics may have DDIs due to the changes of their blood-concentrations. Calcineurin inhibitors, including CS, may interact with either corticosteroids or statins and is usually metabolized by CYP450 subfamily enzyme.[1,18,20,21] However, even its broad applications, there has not been any specific study conducted on the interactions between CS and cefepime. Moreover, it was not wholly investigated whether ciprofloxacin or cefepime induces or inhibits CYP3A4 enzyme in the metabolic system. Therefore, the blood-concentration of CS could be affected by various factors, and might be resulted from the connection to the pathophysiological conditions of the patients.[14,22] [2] Our study demonstrated that the alterations in levels of hepatic indicators due to conversion from ciprofloxacin to cefepime. To a certain extent, this result is coincident with a study that explains replacing antibiotics can affect liver functions.[23] We have found that 71% of patients with aggravated hepatic function had increased blood-level of CS; but patients with normal function, the blood-concentration was not maintained constantly. [3] When an initial antibiotic was changed by other class, the blood-concentration of CS was increased with statistical significance (p=0.0261). The average incremental ratios of CS concentration were 78.6% in the T-bil augmented group, 76.9% in AST augmented group, and 87.5% in ALT augmented group; In groups with a paired augmented levels such as T-bil-AST, T-bil-ALT and AST-ALT, the incremental ratio of CS concentration was 85.7%, 100.0% and 100.0%, respectively; Finally, the ratio was 100.0% in group that has all the augmented values in T-bil, AST, and ALT. [4] When cefepime is applied against NPF after HSCT, the blood-concentration of CS may be increased concurrently in patients with diminished hepatic conditions. Therefore, clinicians need to regulate a dosing amount of CS in order to secure therapeutic outcomes and to prevent adverse reactions.[24]

In spite of these demonstrations, this study has some limitations. On condition that we found cefepime can increase the blood-concentrations of CS, due to difficulty in gathering sufficient study subjects, those facts were based on a small size of study sample. Metabolic mechanisms to a certain medication usually depend on population-pharmacokinetics and/or pharmacogenomic properties that will constantly discover new findings relate to ethnic diversity. However, this research was performed only subject in one university hospital and

these findings could not be adopted in general. Another potential limitation is that the alterations on blood-concentration of CS, which possibly arise from complex interactions with other medications did not be investigated as well as the exact mechanisms of diminished liver functions was not clearly defined.

In conclusion, in the course of treating patients with NPF after HSCT, cefepime had a greater affects on aggravating hepatic functions than ciprofloxacin. Also, as a reason of CS blood-concentration was increased with statistical significance, we propose, about 13% reduction of CS at C_{ss} for patients in lowered hepatic function would be revealed more optimal. However this proposed regimen requires more validation by a further prospective clinical study.

REFERENCES

1. Kelly P, Kahan BD. Review: metabolism of immunosuppressant drugs. Current Drug Metab 2002; 3: 275-87.
2. Venkataramanan R, Swaminatan A, Prasad T, *et al*., Clinical Pharmacokinetics of Tacrolimus. Clin pharmacokinet 1995; 29: 404-30.
3. Jacobson PA, Ng J, Green KG, *et al*., Posttransplant day significantly influences pharmacokinetics of cyclosporine after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2003; 9(5): 304-11.
4. 이주연 . 노인에서의 장기이식 . J Kor Soc Health-Syst Pharm 2011; 28: 230-4.
5. Zeng Y, He YJ, He FY, *et al*., Effect of bifendate on the pharmacokinetics of cyclosporine in relation to the CYP3A4*18B genotype in healthy subjects. Xenobiotica 2009; 30(4): 478-84.
6. Thervet E, Legendre C, Beaune P, *et al*., Cytochrome P450 3A polymorphisms and immunosuppressive drugs. Pharmacogenomics 2005; 6(1): 37-47.
7. Leather HL. Drug interactions in the hematopoietic stem cell transplant (HSCT) recipient: what every transplanter needs to know. Bone Marrow Transplant 2004; 33(2): 137-52.
8. Kutluk T, Kurne O, Akyüz C, *et al*., Cefepime vs. Meropenem as empirical therapy for neutropenic fever in children with lymphoma and solid tumours. Pediatr Blood Cancer 2004; 42(3): 284-6.
9. Antabli BA, Bross P, Siegel RS, *et al*., Empiric antimicrobial therapy of febrile neutropenic patients undergoing haematopoietic stem cell transplantation. Int J Antimicrob Agents 1999; 13(2): 127-30.
10. Mori T, Aisa Y, Kato J, *et al*., Drug interaction between oral solution itraconazole and calcineurin inhibitors in allogeneic hematopoietic stem cell transplantation recipients: an association with bioavailability of oral solution itraconazole. Int J Hematol 2009; 90(1): 103-7.
11. Adriaenssens B, Roskams T, Steger P, *et al*., Hepatotoxicity related to itraconazole: report of three cases. Acta Clin Belg 2001; 56(6): 364-9.
12. Yahav D, Gafter-Gvili A, Muchtar E, *et al*., Antiviral prophylaxis in haematological patients: systematic review and meta-analysis. Eur J Cancer 2009; 45(18): 3131-48.
13. Tam VH, McKinnon PS, Akins RL, *et al*., Pharmacokinetics and Pharmacodynamics of Cefepime in Patients with Various Degrees of Renal Function. Antimicrob Agents Chemother 2003; 47(6): 1853-61.
14. Endimiani A, Perez F, Bonomo RA. Cefepime: a reappraisal in an era of increasing antimicrobial resistance. Expert Rev Anti Infect Ther 2008; 6(6): 805-24.
15. Choi SM, Park SH, Lee DG, *et al*., Current Antimicrobial Usage for the Management of Neutropenic Fever in Korea: A Nationwide Survey. J Korean Med Sci 2008; 23: 941-7.
16. Hughes WT, Armstrong D, Bodey GP, *et al*., 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Clin Infect Dis 2002; 34(15): 730-51.
17. NCCN Practice Guidelines in Oncology - Prevention and treatment of cancer-related infections. Version 2. 2009. http://oralcancerfoundation.org/treatment/pdf/infections-NCCN.pdf. (Accessed on June 30, 2010)
18. Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. Clin pharmacokinet 1998; 35: 361-90.
19. Huangs SM, Lesko LJ, Williams RL. Assessment of the quality and quantity of drug-drug interaction studies in recent NDA submissions: study design and data analysis issues. J Clin pharmacol 1999; 39: 1006-14.
20. Niwa T, Yamamoto S, Saito M, *et al*., Effect of Cyclosporine and Tacrolimus on CYP450 Activities in Human Liver Microsomes. Yakugaku Zasshi 2007; 127(1): 209-16.
21. Choi HA, Choi JY, Park YH, *et al*., Analysis of Drug Interaction between Simvastatin and Cyclosporine. J Kor Soc Health-Syst Pharm 2010; 27: 313-22.
22. Armstrong SC, Cozza KL, Pimentel EA. Immunosuppressants. Psychosomatics 2002; 43:424-27.
23. Micromedex (http://www.micromedex.com/ accessed Dec. 12, 2009)
24. Lee DG, Choi SM, Yoo JH, *et al*., Population pharmacokinetics of cefepime in febrile neutropenic patients. Kor J Clin Pharmacol Ther 2003; 11(1): 23-9.