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Clinical Studies on Plasma Concentrations of Acyclovir Treated in Transplant Patients

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For the treatment and prophylaxis of diseases by herpesvirus, Acyclovir (ACV) is commonly used in transplant patients. However, adverse effects such as neurotoxicity have been reported. The plasma concentrations of ACV were studied in the transplant patients and the relationships between the plasma concentration of ACV and the renal function were examined. The dose-adjusted plasma ACV level showed significant correlations with serum creatinine, creatinine clearance (Clcr) and BUN. The recommendations for dose reductions of oral ACV have been indicated in the patients with Clcr less than 25 mL/min/1.73m^2. The average of the dose-adjusted plasma ACV concentrations of the patients with Clcr between 25 and 70 mL/min was about 2 times of that with Clcr more than 70 mL/min. In addition, the comparison of the measured to predicted plasma ACV concentrations, which were calculated using the pharmacokinetic parameters, indicated that the mean absolute error was greater in the patients with Clcr less than 70 mL/min than those with Clcr more than 70 mL/min. It is suggested that it may be necessary to monitor the plasma concentration of ACV, clinical state and renal function especially in the patients with Clcr less than 70 mL/min.

KeyWords : Acyclovir, Renal function, Transplantation, Adverse Reactions

Introduction

Acyclovir (ACV) selectively inhibits viral DNA polymerase, thus preventing replication of the virus with little effect on the mammalian cell function. ACV has been used for the treatment and prophylaxis of herpes simplex and varicella-zoster viral infections. In general, ACV is well tolerated with nausea, vomiting and diarrhea being the most commonly reported adverse effects. However, neurotoxicity and nephrotoxicity have also been reported. We experienced the occurrence of neurologic symptoms probably ascribable to ACV in one transplant patient. Thereby, the plasma concentrations of ACV were retrospectively studied in the transplant patients. Because ACV is predominantly renally excreted, we examined the relationship between the concentration of ACV and the renal function.

Materials and Methods

Between November 1999 and June 2001, the plasma concentrations of ACV, the whole blood concentrations of cyclosporin (CyA) or tacrolimus (FK506) and the laboratory data of eleven transplant patients (male/female 6/5, age 33.7 ± 17.4 years, mean ±S.D.) were studied. The study protocol was approved by our Ethics Committee at Yamagata University. These patients had received renal transplants (n=5), bone marrow transplants (n=5) and a peripheral blood stem cell transplant (n=1). They orally received ACV (200 − 1200 mg/day) for a prophylaxis along with the immunosuppressant CyA (75 − 450 mg/day, n = 8) or FK506 (0.15 − 10 mg/day, n = 3). Blood

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samples were collected 9 − 12 hours after the administration of these agents (4.9 ± 2.3 samples were collected in the separate days per one patient). This investigation was done at 0-3 months after the transplantation except for one patient. The laboratory data consisted of serum creatinine (Scr), blood urea nitrogen (BUN), glutamic pyruvic transaminase (GPT), triglyceride (TG), white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb) and platelets (Plt).

Sample analysis

The plasma concentration of ACV was assayed by a high-performance liquid chromatographic method [1], the whole blood concentration of CyA was assayed by fluorescence polarization immunoassay (FPIA, TDX, Dainabot, Tokyo, Japan) and FK506 was assayed by microparticle enzyme immunoassay (MEIA, IMx, Dainabot, Tokyo, Japan). ACV was purchased from GlaxoWellcome (Osaka, Japan). All other reagents were of analytical-reagent grade. The chromatographic system consisted of a DP-8020 pump, UV-8020 spectrophotometer and AS-8021 autosampler (TOSOH, Tokyo, Japan). The TSK gel ODS-80TM (4.6 mm × 15 cm, TOSOH, Tokyo, Japan) was used for the column. The mobile phase was a mixture of 1/15M potassium dihydrogenphosphate (pH2.75) and acetonitrile (97:3). The wavelength was set at 250 nm and the flow rate was 0.8 mL/min. The calibration curve of ACV was linear in the concentration range 0.05-20 μg/mL (the correlation coefficient 0.989). The recovery rate was 99.4%, coefficient variation was less than 2 %, and detection limit was 0.02 μg/mL.

Data analysis

The Creatinine clearance (Clcr) was calculated from the body weight, age, serum creatinine level, and gender, using Cockcroft's formula [2]. The predicted plasma ACV concentrations were calculated using the reported pharmacokinetic parameters [3].

The parameter values included the volume of distribution of 69 L/1.73m^2, an absorption rate constant of 1.3 hr^{-1}, an elimination rate constant equal to 0.0025 ×Clcr + 0.021 hr^{-1} and an absolute bioavailability of 0.2. The predicted plasma concentrations were designed using a one-compartment model. All data are expressed as the mean±S.D. Pearson correlation test was employed for a correlation and the differences between groups were tested for statistical significance by the multiple comparison test (Bonferroni/Dunn test).

Results

The plasma concentrations of ACV were 0.87± 1.13 μg/mL (range 0.05-6.87 μg/mL). ACV has been used for a prophylaxis of herpes simplex virus in the transplant patients, it was reported that ID_{50} of ACV against herpes simplex virus type I was 0.023 μg/mL and that of herpes simplex virus type II was 0.032 μg/mL[4,5]. The levels of ACV were higher than ID_{50} of ACV against herpes simplex virus in our study.

Statistically significant correlations were found between the dose-adjusted plasma ACV concentrations and serum creatinine or BUN (Fig.1). The dose-adjusted plasma ACV concentrations of the patients with Clcr less than 25 mL/min were significantly higher than those with Clcr more than 70 mL/min. Although the dose reduction of oral ACV is only recommended in the patients with Clcr less than 25mL/min/1.73m^2, the average of the dose-adjusted plasma ACV concentrations of the patients with Clcr between 25 and 70 mL/min was about 2 times of that with Clcr more than 70 mL/min (Fig.2).

The comparison of the measured to the predicted plasma ACV concentrations using the pharmacokinetic parameters[3] indicated that the predictability was almost suitable (Fig.3). However, the absolute errors (AE) between the measured and predicted concentrations were different in a grade of renal function; AE with Clcr more than 70 mL/min were 0.34±0.30 μg/mL (n=22), AE with Clcr between 25 mL/min and 70 mL/min were 0.84±1.41 μg/mL (n=24), AE with Clcr less than 25 mL/min were 1.24±1.00 μg/mL (n=8). Thus, AE with Clcr less than 70 mL/min were greater than those with Clcr more than 70 mL/min.

CyA has an adverse effect on the renal dysfunction. It was reported that the

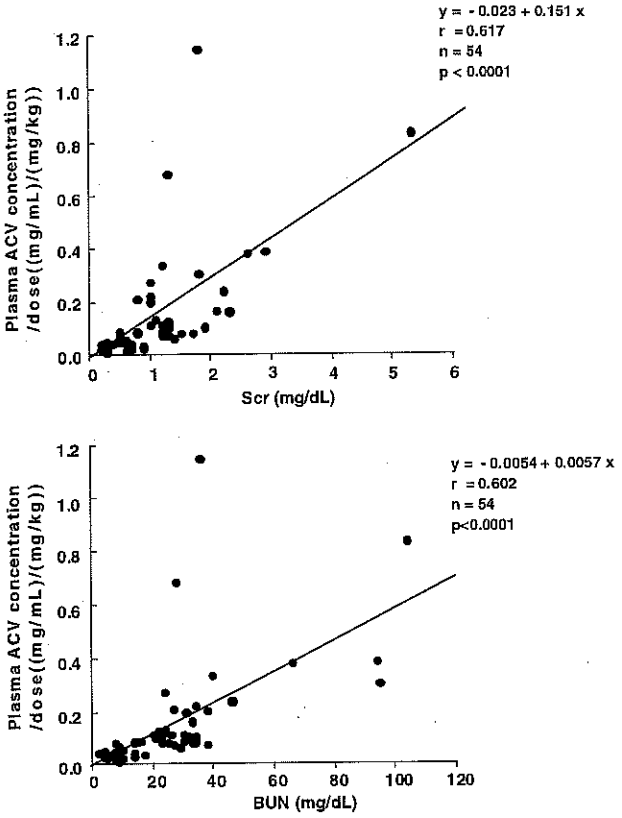

Figure 1. Correlation between dose-adjusted plasma acyclovir (ACV) concentrations and serum creatinine (upper panel) or BUN (lower panel).

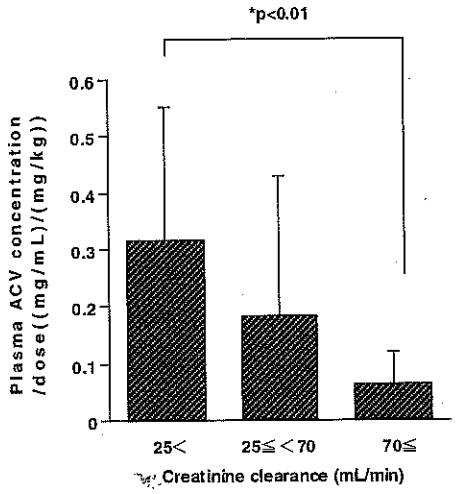

Figure 2. Comparison of dose-adjusted plasma acyclovir (ACV) concentration by creatinine clearance.Mean±S.D.

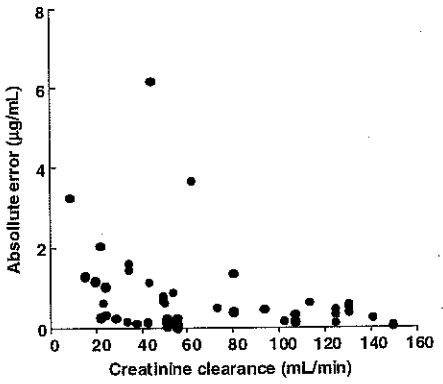

Figure 3. Absolute error between measured and predicted plasma concentrations of acyclovir (ACV)(n=54).

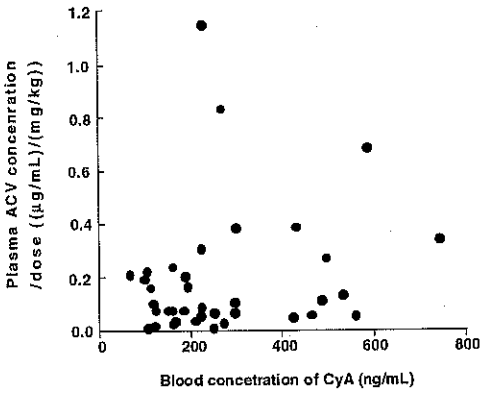

Figure 4. Correlation between dose-adjusted plasma acyclovir (ACV) concentrations and blood cyclosporin (CyA) concentrations (n=54).

nephrotoxicity occurred with trough serum CyA levels of more than 200 ng/mL in the renal transplant patients[6]. Thereby, a high blood concentration of CyA may impair the renal function and may cause an elevation in the plasma ACV concentration. However, no significant correlation was found between the blood concentrations of CyA or FK506 (data were not shown) and the dose-adjusted plasma concentrations of ACV (Fig.4).

ACV has produced the adverse effects of bone marrow suppression, liver dysfunction, hyperglycemia, etc. However, no significant correlations were found between the plasma ACV concentrations and WBC, RBC, Hg, Plt, GPT and TG levels (data were not shown).

Discussion

Although adverse effects due to ACV rarely occur, neurotoxicity is a potentially serious consequence of the administration of this agent. As ACV is predominantly renally excreted[7], neuropsychiatric adverse effects have been reported in patients with renal impairment. Adair et al. [8] reviewed 30 cases of ACV neurotoxicity, and found that the impaired renal function was present in 21 of 30 patients, in 9 patients that received hemodialysis and in 6 patients that received peritoneal dialysis.

To prevent the adverse effects, recommendations for dose reductions of oral ACV have been indicated. The recommended dosing adjustments for oral ACV are as follows: for the treatment of varicella-zoster, Clcr > 25 mL/min/1.73m^2, 800mg, five times daily; Clcr range 25 to 10 mL/min/1.73m^2, 800mg, tree times daily; Clcr < 10 mL/min/1.73m^2, 800mg, twice daily, and for the treatment of herpes simplex, Clcr ≧ 10 mL/min/1.73m^2, 200mg, five times daily; Clcr < 10 mL/min/1.73m^2, 200mg, twice daily.

However, neurotoxicity was reported in patients who were administered ACV according to the recommendations. Neurotoxicity occurred for oral ACV 200mg/day[9] and on 800mg, twice daily[10,11] in the patients with terminal renal failure. Fletcher et al. [3] administered ACV to twelve renal transplant patients according to the regimen which was almost the same as the manufacturer's recommendation, and found neurotoxicy occurred in one patients (minimum plasma concentration (Cmin) of ACV was 88.5 μmol/L), and a fluctuation in the serum creatinine levels (serum creatinine level increased from 1.8 to 3.7 mg/dL, Cmin of ACV was 30.5 μmol/L) occurred in one patient. They also reported that the average Cmin of ACV in each renal function group was 8.0- 26.5 μmol/L [3]. According to the suggestion that a plasma concentration of ACV greater than 20 μmol/L (4.5 μg/mL) is associated with neuropsychiatric manifestations[12], there might be several patients whose plasma ACV concentrations were in the toxic range.

In our investigation, the dose-adjusted plasma ACV levels showed statistically significant correlations with the serum creatinine, BUN or Clcr. The average of the dose-adjusted plasma ACV concentrations of the patients with Clcr between 25 and 70 mL/min was about 2 times of that with Clcr more than 70 mL/min. In addition, the mean absolute errors between the measured and predicted ACV concentrations were greater in the patients with Clcr less than 70 mL/min than those with Clcr more than 70 mL/min. As a result, it is suggested that the administration of ACV according to the recommendations is not always safe, especially in the patients with Clcr less than 70 mL/min.

Furthermore, it is suggested that marrow transplant patients may have increased risk of neurologic adverse effects. Neurotoxicity was observed in six marrow transplant patients with normal renal function[13], and reversible brain MRI changes probably associated with ACV toxicity were observed in a 12-year-old girl after stem cell transplant[14]. Marrow transplant patients are administered ACV in combination with immunosuppressants and other drugs. CyA and FK506, the immunosuppressant drugs, have adverse reactions such as neurotoxicity and nephrotoxicity. Also, the chemotherapy or irradiation before a marrow transplant is likely to cause neurotoxicity and nephrotoxicity.

Renal insufficiency associated with ACV has been reported in a patient with normal renal function[15-17]. Animal studies suggest that renal injury is attributable to intrarenal obstruction secondary to ACV crystal formation in the collecting ducts. However, acute tubular necrosis and the absence of crystalluria or crystal deposition within the biopsy specimen were reported[16]. In our investigation, there was a patient whose serum creatinine abruptly elevated, possibly ascribable to CyA, the myeloablative conditioning regimen or ACV. Nephrotoxicity may occur in patients without renal insufficiency and the more careful monitoring of the renal functions and plasma concentrations of ACV may be necessary when renal functions abruptly deteriorate.

It was reported that neurotoxicity developed with a delay of 24 to 48 hours after the ACV peak serum concentration, and it could be explained by the fact that equilibration between the blood and

brain is very slow [15]. Therefore, it may be necessary to measure the plasma concentration of ACV in series together with the careful monitoring of the clinical state, renal functions and co-administered drugs.

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