Inhibition of Theophylline Metabolism by Aciclovir

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We report a case of side effects caused by the increase in plasma theophylline concentration after coadministration of aciclovir had been started during theophylline therapy. Interaction between theophylline and aciclovir has not previously been reported. Therefore, a study of the pharmacokinetic and metabolic interactions between theophylline and aciclovir was carried out in five healthy male volunteers. All subjects received a single oral dose of 320 mg theophylline (aminophylline, 400 mg) after they had taken oral aciclovir 800 mg five times daily for two consecutive days. The area under the curve from 0 to infinity of theophylline (AUC₀–∞) after coadministration of aciclovir was increased from 189.9 ± 18.2 to 274.9 ± 34.3 μg·h/ml (p < 0.01), and total body clearance was decreased from 28.4 ± 2.9 to 19.8 ± 2.5 ml/h/kg (p < 0.01). Further, there was a significant increase in urinary theophylline and decreases in urinary 1,3-dimethyluric acid and 1-methyluric acid after coadministration of aciclovir. The decrease in total body clearance is likely to have resulted from inhibition of metabolism via the oxidation pathway.

The results indicated that with aciclovir therapy lower doses of theophylline might be necessary and careful monitoring of plasma concentrations was essential.

Key words theophylline; aciclovir; drug interaction; drug metabolism; metabolic clearance; metabolic inhibition

Theophylline is widely used in the treatment of patients with reversible obstructive airway diseases, and is a bronchodilator eliminated from the body by transformation in the liver to inactive metabolites. Aciclovir, a guanine derivative, is reported to exhibit strong antiviral activity toward viruses of the herpes group and is largely excreted in the urine as an unchanged drug. Theophylline and aciclovir occasionally are coadministered to treat patients with chronic or obstructive pulmonary disease and herpes diseases.

We experienced a patient who exhibited an increase in plasma theophylline concentration following initiation of aciclovir therapy. The interaction with theophylline is clinically important because of its narrow therapeutic range and serious toxic effects; for example, the interaction between theophylline and cimetidine is well known. The interaction between theophylline and aciclovir, however, has not yet been reported. The present study was performed to evaluate the influence of aciclovir on the pharmacokinetics and metabolism of theophylline in healthy male volunteers.

MATERIALS AND METHODS

Materials Neophylline® (aminophylline, 100 mg tablet; Eisai, Tokyo, Japan), equivalent to 80 mg theophylline; and Zovirax® (aciclovir, 400 mg tablet; Wellcome, Osaka, Japan) were used. 1-Methyluric acid (1-MU), 3-methylxanthine (3-MX), 1,3-dimethyluric acid (1,3-DMU), and theophylline were purchased from Sigma Chemical Co., Ltd. (St. Louis, MO, U.S.A.), 7-(2-Hydroxyethyl)theophylline (internal standard; I.S.) were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). All other chemicals and solvents were of analytical grade.

Subjects Five male volunteers (four healthy hospital pharmacists and a healthy doctor of internal medicine) aged 27 to 36 years (mean: 30.8 ± 3.3 years) and weighing 54 to 64 kg (mean: 60.0 ± 3.6 kg), participated in the study. Informed consent was obtained from all subjects. Only one was a smoker (< 10 cigarettes/d). Pre-study physical examination and pre- and post-drug laboratory findings (liver and kidney function) were normal. None of the subjects was given any drug other than theophylline and aciclovir during the study.

Study Design The study design of theophylline-aciclovir interaction is shown in Table 1. The study was of the crossover type, with each subject serving as his own control. Subjects abstained from xanthine-containing foods and beverages (e.g., coffee, tea, cola, and chocolate) for 2 d prior to each sampling period. Each subject initially received a single oral dose of Neophylline® 400 mg (100 mg tablet × 4) with 200 ml water at 9:00 a.m. This was the control trial during which aciclovir was not coadministered. Next, after a washout period of 13 d, aciclovir was administered in doses of 800 mg (400 mg tablet × 2) five times daily (9:00, 12:00, 15:00, 19:00, and 22:00) for 2-d period. On the morning of day 15 (9:00 a.m.), each subject received 400 mg aminophylline with 200 ml water in combination with aciclovir. Blood samples of 5 ml were collected from the contralateral arm in tubes containing EDTA-K2, before the administration of theophylline and 0.5, 1, 2, 4, 6, 8, 12, and 24 h after theophylline administration. The blood was immediately centrifuged and the plasma separated. Urine samples were collected during the 0—3, 3—6, 6—9, 9—12, and 12—24 h period.

Table 1. Study Design of Theophylline–Aciclovir Interaction

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O, theophylline 320 mg p.o.; ●, aciclovir 800 mg p.o.

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periods after theophylline administration. Blank urine samples were obtained in advance to check for any interference with the analysis and to prepare calibration curves for determination of theophylline and its metabolites. Plasma and urine samples were stored at −30°C until assayed.

**Analytical Techniques** The plasma concentrations of theophylline were determined in duplicate using a fluorescence polarization immunoassay (FPIA, TDX, Dainabot Co., Ltd., Tokyo, Japan) with within-run and within-day coefficients of variation of less than 5%. The urinary concentrations of theophylline and its metabolites were measured by the modified method of Kubo et al., using an HPLC (Tosoh Co., Ltd., Tokyo, Japan) equipped with a spectrophotometric detector (UV-8020) set at 280 nm, a dual pump (CCPS), a marker generator (VC-8020), and an autosampler (AS-8020). Two hundred fifty microliters of methanol containing 4 μg/ml of 7-(2-hydroxyethyl)theophylline (I.S.) was added to 50 μl of urine sample. The mixture was centrifuged at 10,000×g for 5 min at 4°C and 20 μl of the supernatant was injected into the HPLC. The mobile phase was acetonitrile-0.01 M sodium acetate buffer adjusted to pH 4 (1:10, v/v). A Senshu Pak column (ODS-2251-D,6×250 mm i.d., Senshu Kagaku Co., Ltd., Tokyo, Japan) was used, and flow-rate was 1 ml/min. The retention times of aciclovir, 1-MU, 3-MX, 1,3-DMU, theophylline, and I.S. were 6.2, 6.8, 7.3, 9.3, 15.0, and 19.2 min, respectively. A chromatogram is shown in Fig. 1. Calibration curves were obtained from blank urine samples spiked with standards of theophylline and its metabolites. Aciclovir did not interfere with the analysis.

**Pharmacokinetic Analysis** Unweighted plasma concentrations (C) of theophylline were fitted to a compartment open model as follows:

\[
C = \frac{K_d \times F \times D}{V_d \times (K_e - K_i)} (e^{-K_e \times t} - e^{-K_i \times t})
\]

where \(K_e\) is the apparent first order absorption rate constant (h⁻¹), \(K_i\) is the apparent first order elimination rate constant (h⁻¹), \(V_d\) is the volume of distribution (l/kg), \(F\) is the bioavailable fraction of the dose, which is assumed to be 1.0, and \(t\) is the time after administration (h). Total body clearance (CL) and renal clearance (CLR) were determined as follows:

\[
CL = \frac{\text{dose/AUC}_{0-\infty}}
\]

\[
CLR = \frac{X_{t_{0-24}}/AUC_{0-24}}
\]

where \(X_{t_{0-24}}\) is the 24 h urinary recovery of theophylline and \(AUC_{0-\infty}\) and \(AUC_{0-24}\) are the area under the curve from 0 to infinity and from 0 to 24 h after dosing, respectively. The metabolic clearance (CLM) was calculated as \(CL_M = CL_T - CL_R\). The formation clearance \(CL_{f}\) of each metabolite (\(CL_{1,1-MU}, CL_{1,3-MX},\) and \(CL_{1,3,3-DMU}\)) was estimated as \(f_i \times CL_M\), where \(f_i\) is the fractional urinary recovery rate of each metabolite, which was recorded as a percentage of the 24 h recovery of the three metabolites. The quantity of metabolites excreted in urine was expressed in molar units in order to maintain equivalence to theophylline.

The appropriate values of various pharmacokinetic parameters were calculated by the iterative non-linear least squares fitting computer program (MULTI), adapted for the personal computer PC-9801 DS (NEC Co., Ltd., Tokyo, Japan).

**Statistical Analysis** Data are expressed as mean ± standard deviation. Statistical analysis was performed using the paired Student’s t-test.

**RESULTS**

**A Case Report** A 64-year-old woman weighing 45 kg was hospitalized with bronchial asthma. She had been receiving a slow-release theophylline preparation (Theodur® 200 mg twice a day (8:30, 18:30) for 10 d. Bronchospasms had been not controlled with this dose, because plasma concentration (2 h before the dose; 6:30 a.m.) was 4.96 μg/ml (normal therapeutic range 10—40 μg/ml), and the theophylline dose was increased to 200 mg three times daily (8:30, 12:30, 18:30) (Fig. 2).
At the same time she had a herpes simplex, and aciclovir was coadministered five times daily (8:30, 12:30, 15:00, 18:30, 21:00) for 5 d. A few days later the patient developed depression and irritation like a panic disorder. Five days after coadministration of the theophylline and aciclovir, her plasma theophylline level was 17.15 µg/ml (6:30 a.m.). Aciclovir therapy was ended, and maprotiline (Ludomi®) at 10 mg three times daily and alprazolam (Solanax®) at 0.4 mg three times daily were coadministered; the depression and irritation gradually disappeared. Nine days later, the plasma concentration of theophylline was 12.70 µg/ml (6:30 a.m.).

**Effect of Aciclovir on Theophylline Disposition** The plasma theophylline concentration–time profiles in the five subjects, with and without the coadministration of aciclovir, show that the concentration after coadministration of aciclovir was higher than that of monotherapy (Fig. 3). By coadministration of aciclovir, the 24 h plasma theophylline concentration after administration of theophylline was increased from 2.8 ± 0.3 to 4.3 ± 0.3 µg/ml (p < 0.01). The time profiles of the urinary recovery of theophylline and its metabolites with concurrent drug treatment are shown in Fig. 4. There were significant differences between monotherapy and coadministration with aciclovir in the 24 h urinary recovery of theophylline, 1-MU, and 1,3-DMU. After pretreatment with aciclovir, the urinary recovery of 1-MU, 3-MX, and 1,3-DMU (mean ± S.D.) decreased from 55.8 ± 29.8 to 30.3 ± 25.1 mg (p < 0.05), from 18.8 ± 7.5 to 12.5 ± 5.0 mg, and from 102.7 ± 17.6 to 76.5 ± 16.4 mg (p < 0.05), respectively, and that of theophylline increased from 44.8 ± 8.0 to 66.3 ± 19.1 mg (p < 0.05).

The kinetic parameters of theophylline and its metabolites in the presence and absence of aciclovir are shown in Table 2. Aciclovir significantly increased the $AUC_{0-\infty}$, $K_a$, $T_{1/2}$, and $CL_R$ of theophylline, while significantly decreasing the $K_e$, $CL_T$, and $CL_M$, and concurrently reduced the formation clearances ($CL_{1-MU}$, $CL_{3-MX}$, and $CL_{1,3-DMU}$) of its metabolites. No change in $V_d$ was found, irrespective of aciclovir treatment.

**DISCUSSION**

This study clearly showed that aciclovir significantly reduces the total body theophylline clearance (24.6–37.5%, mean 30.6 ± 5.1%). Upton reported that the total body theophylline clearance was significantly decreased by enoxacin (42–74%), erythromycin (5–35%), cimetidine (8–39%), verapamil (14–23%), diltiazem (12–21%), allopurinol (21%), ticlopidine (37%), etc. The interaction between theophylline and these drugs is of major clinical importance, and in the present study, aciclovir was added as a drug affecting theophylline disposition.

It is generally known that theophylline is eliminated mainly by biotransformation via the liver mixed function oxidase system and is excreted in urine as 1-MU, 3-MX, 1,3-DMU, and unchanged theophylline. More recently, it has been shown that theophylline is mainly metabolized by cytochrome P-4501A2 in humans; its metabolic pathway is shown in Fig. 5.

Konishi et al. reported that enoxacin led to decreases of 59%, 69%, and 38% in the formation clearance of the three theophylline metabolites, 1-MU, 3-MX, and 1,3-

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Fig. 2. A Case Report of Side Effects Caused by the Increase in Plasma Theophylline Concentration after Coadministration of Aciclovir Began

Fig. 3. Plasma Theophylline Concentration–Time Profiles in the Five Subjects with and without the Coadministration of Aciclovir

Theophylline alone (○), coadministration of theophylline and aciclovir (●). Each point represents mean ± S.D. a) $p < 0.01$. 
DMU, respectively, in the interaction between theophylline and enoxacin. Moreover, Takagi et al.\textsuperscript{11)} reported that a decrease in the total body clearance of theophylline during coadministration of enoxacin resulted from inhibition of the 1-demethylation metabolic pathway.

In our study, after treatment with aciclovir, the formation clearances of 1-MU, 3-MX, and 1,3-DMU, calculated from their urinary recoveries showed significant decreases of 58\%, 40\%, and 37\%, respectively (Table 2). Based on the results of total urinary excretion of theophylline and its major metabolites, there were significant decreases in urinary 1,3-DMU and 1-MU after coadministration of aciclovir. It is therefore proposed that the decrease in total body clearance of theophylline when coadministered with aciclovir may be a result of inhibition of metabolism via the oxidation pathway.

In contrast, aciclovir is principally excreted in an
unchanged form in the urine, and a portion of it (9-[(2-hydroxyethoxy)methyl]guanine) is metabolized and excreted as 9-carboxymethoxymethyl-guanine in the urine. 12) Aciclovir is administered for 5 or 7 d in the therapy of herpes simplex or herpes zoster virus infection. Therefore, theophylline accumulation when coadministered with aciclovir may be only for a short period, but caution is necessary.

From the results of our study, we suggest that the dosage of theophylline should be reduced in coadministration of aciclovir in order to assure safe therapy, with routine monitoring of plasma theophylline concentrations and side effects.

REFERENCES