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Influences of Pyrexia and Age on Theophylline Clearance in Young Children with Asthma

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ABSTRACT

Fifty hospitalized children with asthmatic bronchitis and bronchial asthma were treated with a continuous intravenous drip infusion of aminophylline. To investigate the pharmacokinetics of theophylline in the presence of pyrexia, patients were divided into two groups based on body temperature: a pyrexia group (≥ 38°C) and a non-pyrexia group (< 38°C). Theophylline clearance was 0.064 ± 0.017 liters/kg/hr in the non-pyrexia group and 0.049 ± 0.010 liters/kg/hr in the pyrexia group. Theophylline clearance in the non-pyrexia and pyrexia groups was 0.044 ± 0.007 liters/kg/hr and 0.030 ± 0.009 liters/kg/hr (≤ 6 months), 0.071 ± 0.011 liters/kg/hr and 0.047 ± 0.008 liters/kg/hr (6 to ≤ 12 months), 0.084 ± 0.012 liters/kg/hr and 0.055 ± 0.006 liters/kg/hr (1 to ≤ 2 years), and 0.065 ± 0.007 liters/kg/hr and 0.051 ± 0.001 liters/kg/hr (2 to ≤ 3 years), respectively. In all age groups, theophylline clearance of the pyrexia group was significantly less than that of the non-pyrexia group ($p < 0.01$), showing that there was a significant pharmacokinetic difference in theophylline clearance between the groups. Multivariate statistical analysis showed that theophylline clearance was affected by pyrexia and age. This study showed that the presence of pyrexia decreases theophylline clearance, and that it affects theophylline clearance in an age-dependent manner. Based on the results of this study, dosages should be designed based on the clearance at the time of pyrexia.

Key words: *Theophylline, Children, Pyrexia, Clearance*

Aminophylline is widely used for the treatment of respiratory illnesses, including asthma. However, the therapeutic range of serum concentrations of theophylline is narrow, and overdosage readily leads to various adverse reactions, including nausea, vomiting, tachycardia, abdominal bloating, and spasms[4,7]. Therefore, serum concentrations of theophylline must be maintained within a relatively narrow range to achieve optimal therapeutic benefit, while avoiding toxic side effects. In addition, theophylline clearance is affected by combined medicine or by the complications of illness[10]. Furthermore, because theophylline clearance shows significant inter-individual variation, therapeutic drug monitoring (TDM) is essential to achieve efficacy with this drug and to avoid toxicity.

The rate of theophylline clearance changes with age[2,5,6,8,9], making it particularly difficult to determine the dosage in children. It has been reported that the pharmacokinetics of theophylline in children changes at the time of infection when accompanied by pyrexia, leading to an increase in serum concentration of the drug[3,11,12,14,15]. Accurate pretreatment estimation of serum theophylline concentrations in young children at the time of pyrexia is considered to be extremely important for controlling asthma attacks while minimizing adverse reactions. It is very important to determine theophylline clearance rates according to the age of the patient at the time of pyrexia to design a suitable treatment plan and the initial dose of theophylline.

Although it has been reported that theophylline clearance is affected by age and pyrexia, there is no report demonstrating the effect of age at the time of the pyrexia on theophylline clearance.

In the present study, we determined theoph-

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ylline clearance according to the age at the time of pyrexia and investigated the effects of pyrexia on the pharmacokinetics of the drug.

MATERIALS AND METHODS

Subjects

Study subjects included 50 children (age, 3 months to 2.9 years) with asthmatic bronchitis and bronchial asthma who were admitted to the pediatrics department of Kosei General Hospital between March 2001 and March 2009. Informed consent was obtained from all of the subjects' families and the Institutional Review Board of Kosei General Hospital approved the study. Subjects were treated with a continuous intravenous infusion of aminophylline (Neophyllin®; Eisai K.K, Tokyo, Japan). Characteristics of the subjects are shown in Table 1. To avoid any potential pharmacokinetic interactions with theophylline, patients did not take any other medication. Liver function tests showed that aminotransferase levels were normal in all patients. None of the patients had heart disease.

Sample Analysis

Venous blood samples were obtained after the second day of continuous intravenous aminophylline infusion, when theophylline levels had almost reached a steady state. Vacuum blood collection tubes without heparin or a serum separating gel was used to draw 1 ml of blood. Blood samples were centrifuged at 3000 rpm for 10 min at room temperature. Serum theophylline concentrations were determined using the Dimension Xpand (Siemens Healthcare Diagnostics, Tarrytown, NY) automated latex immunoagglutination inhibition technique autoanalyzer.

Calculation Method of Theophylline Clearance

This allows calculation of the average serum theophylline concentration at steady state after continuous aminophylline infusion Expression 1:

$$Css = \frac{D}{CL \times Wt} \quad (1)$$ [13]

where Css (μg/ml) is the average serum concentration at the time of continuous intravenous infusion; D (mg/hr) is the dosage per unit time during intravenous infusion; Wt (kg) is the weight; and CL (liter/kg/hr) is the clearance rate. CL can be calculated by Expression 2. A dosage of aminophylline (1 A = 250 mg/10 ml), dissolved in 500 mL of infusion solution, was assumed to be A (ml), and the drip infusion speed was assumed to be B (ml/hr). The aminophylline contained about 80% theophylline (0.8).

$$CL = \frac{25(mg/ml) \times A(ml)/500(ml) \times B(ml/hr) \times 0.8}{Wt \times Css} \quad (2)$$

Examining the Pharmacokinetics of Theophylline in Pyrexia

To investigate the pharmacokinetics of theophylline in the presence of pyrexia, patients were divided into two groups based on body temperature: a pyrexia group (≥ 38°C) and a non-pyrexia group (< 38°C). Moreover, patients were divided into four groups based on age (≤6 months; 6 to ≤ 12 months; 1 to ≤ 2 years; 2 to ≤ 3 years). We studied the difference in theophylline clearance in each group.

Statistical Analysis

Results are presented as means ± standard deviation (S.D.). Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Student's t test for two groups. ANOVA followed by Dunnett's test was used to determine the significance of the difference between groups. A multivariate analysis (quantification theory type I) was performed to analyze the relationship between theophylline clearance and pyrexia. Theophylline clearance was used as the response variable, and other variables (sex, age and fever) used as the explanatory variable.

In all analyses, p values of < 0.05 were considered to be statistically significant.

Table 1. Patient backgrounds

Age group	*≤ 6 months*		*6 to ≤ 12 months*		*1 to ≤ 2 years*		*2 to ≤ 3 years*	
	Pyrexia	Non-pyrexia	Pyrexia	Non-pyrexia	Pyrexia	Non-pyrexia	Pyrexia	Non-pyrexia
n	3	7	8	7	10	5	4	6
Male	2	4	5	4	5	5	2	5
Female	1	3	3	3	5	-	2	1
Weight (kg)	6.9 ± 1.3	7.0 ± 0.5	9.5 ± 1.3	8.6 ± 2.0	10.6 ± 1.4	11.2 ± 1.3	12.8 ± 1.0	13.7 ± 1.7
Dose (mg/kg/hr)	0.4 ± 0.1	0.4 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.8 ± 0.1

n: number of patients

RESULTS

Effect of Pyrexia on Theophylline Clearance

Comparison of the non-pyrexia and pyrexia groups is shown in Fig. 1. Theophylline clearance was significantly lower in the pyrexia group compared to the non-pyrexia group ($p < 0.01$).

The effect of pyrexia on theophylline clearance in the four groups based on age is shown in Fig. 2. For all ages, theophylline clearance was lower in the pyrexia group than in the non-pyrexia group, and this decrease in clearance was significant ($p < 0.01$).

Results of Multivariate Analysis

Table 2 presents the results of the multivariate analysis. Pyrexia and age were indicated to be significant factors that contribute to theophylline clearance.

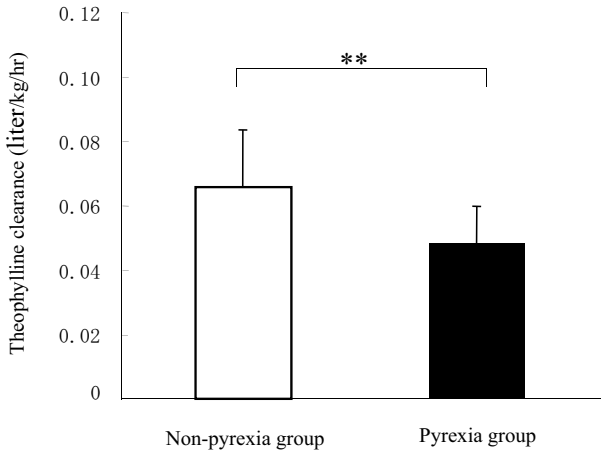

Fig. 1. Effect of pyrexia on theophylline clearance
Each value represents mean ± S.D.
■: Pyrexia group; □: Non-pyrexia group.
**$p < 0.01$ compared with the non-pyrexia group.

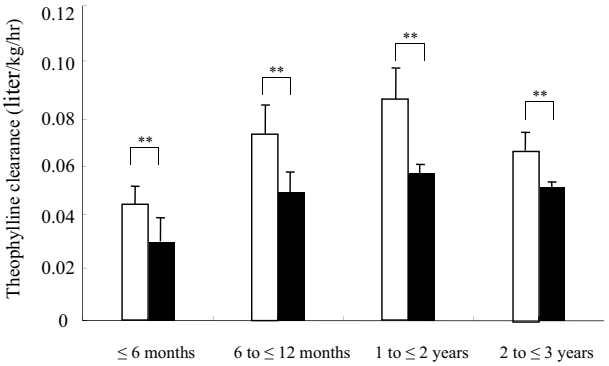

Fig. 2. Effect of pyrexia on theophylline clearance by age
Each value represents mean ± S.D.
■: Pyrexia group; □: Non-pyrexia group.
**$p < 0.01$ compared with the non-pyrexia group.

DISCUSSION

Theophylline clearance was significantly lower in the pyrexia group than in the non-pyrexia group (Fig. 1). The effect of pyrexia on theophylline clearance by age is shown in Fig. 2. There was a significant pharmacokinetic difference in theophylline clearance between the non-pyrexia and pyrexia groups, whereby the presence of pyrexia was found to decrease theophylline clearance. Ichikawa et al[6] studied the clearance of theophylline in young children by measuring this parameter while performing a continuous drip infusion of the drug. The authors reported values of 0.037 ± 0.014 liters/kg/hr (≤ 6 months), 0.058 ± 0.026 liters/kg/hr (6 to ≤ 12 months), 0.061 ± 0.015 liters/kg/hr (1 to ≤ 2 years), and 0.072 ± 0.016 liters/kg/hr (2 to ≤ 3 years). However, the study did not consider the effect of pyrexia on clearance values. Nonetheless, similar to Ichikawa et al, the results of the present study showed that age affects theophylline clearance.

Furthermore, as a result of multivariate analysis, theophylline clearance was found to be affected by pyrexia and age (Table 2). With regard to theophylline dosage in the presence of pyrexia, the American Pediatric Academy[1] reported that it is better to decrease the dosage when pyrexia is present. However, taking into account the fact that there was great individual variation, and in consideration of the treatment and control of asthma, it would be inappropriate to uniformly decrease the dosage of theophylline in all pediatric patients. According to this study, a dosage should be designed based on the clearance at the time of pyrexia and it is necessary that strict control be carried out by TDM.

Results from the findings of earlier studies[14,15] suggest that pyrexia might be a factor that increases serum theophylline concentrations. Furthermore, this study demonstrates that the presence of pyrexia decreases theophylline clearance and is age-dependent. Although, it has been speculated that pyrexia might inhibit hepatic cytochrome P-450[12], the details remain unclear. Yamaguchi et al[15] suggested that cytokines released in the process of acute illness suppress CYP 1A2 activity. Accordingly, further studies

Table 2. Results of multivariate analysis

Explanatory variable	*Category*	*Category score*	*Partial correlation coefficient*
Sex	Male	0.00075	0.11124
	Female	-0.00133	
Age	*≤ 6 months*	-0.02044	0.76237
	6 to ≤ 12 months	0.00363	
	1 to ≤ 2 years	0.00920	
	2 to ≤ 3 years	0.00118	
Fever	Pyrexia	-0.01115	0.77310
	Non-pyrexia	0.01115	

Regression coefficient 0.70890

are necessary in order to optimize the dosage of theophylline administration for children, particularly in cases with pyrexia.

CONCLUSIONS

This study showed that the presence of pyrexia decreases theophylline clearance, and that it affects theophylline clearance in an age-dependent manner. Based on the results of this study, dosages should be designed based on the clearance at the time of pyrexia, and strict control by TDM is necessary to achieve efficacy and to avoid toxicity.

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