CHAPTER IV

RESULTS AND DISCUSSION

Analytical Method

The recovery of theophylline from human plasma after protein precipitation was scattered in ranged of 58% to 72%. These values were determined at concentrations of 1.25, 2.5, 5.0, 10.0, and 20.0 mcg/ml of theophylline in plasma by comparing the area under the chromatogram peaks of theophylline after protein precipitation with those of standard theophylline solution.

Typical chromatograms of theophylline and the internal standard, 8-chlorotheophylline, in a plasma sample and a plasma standard are shown in Figure 4. The chromatograms showed a clear separation between theophylline and 8-chlorotheophylline, of which retention times were approximately 5 and 9 minutes, respectively. Both peaks were sharp and reliable. The region of theophylline and 8-chlorotheophylline observed from human control plasma chromatogram in each experiment (Figure 4), did not show any interference of endogeneous substances.

The standard curves, constructed with each assay, exhibited a good linearity over theophylline concentration range of 1.25 to 20.0 mcg/ml. The correlation coefficients

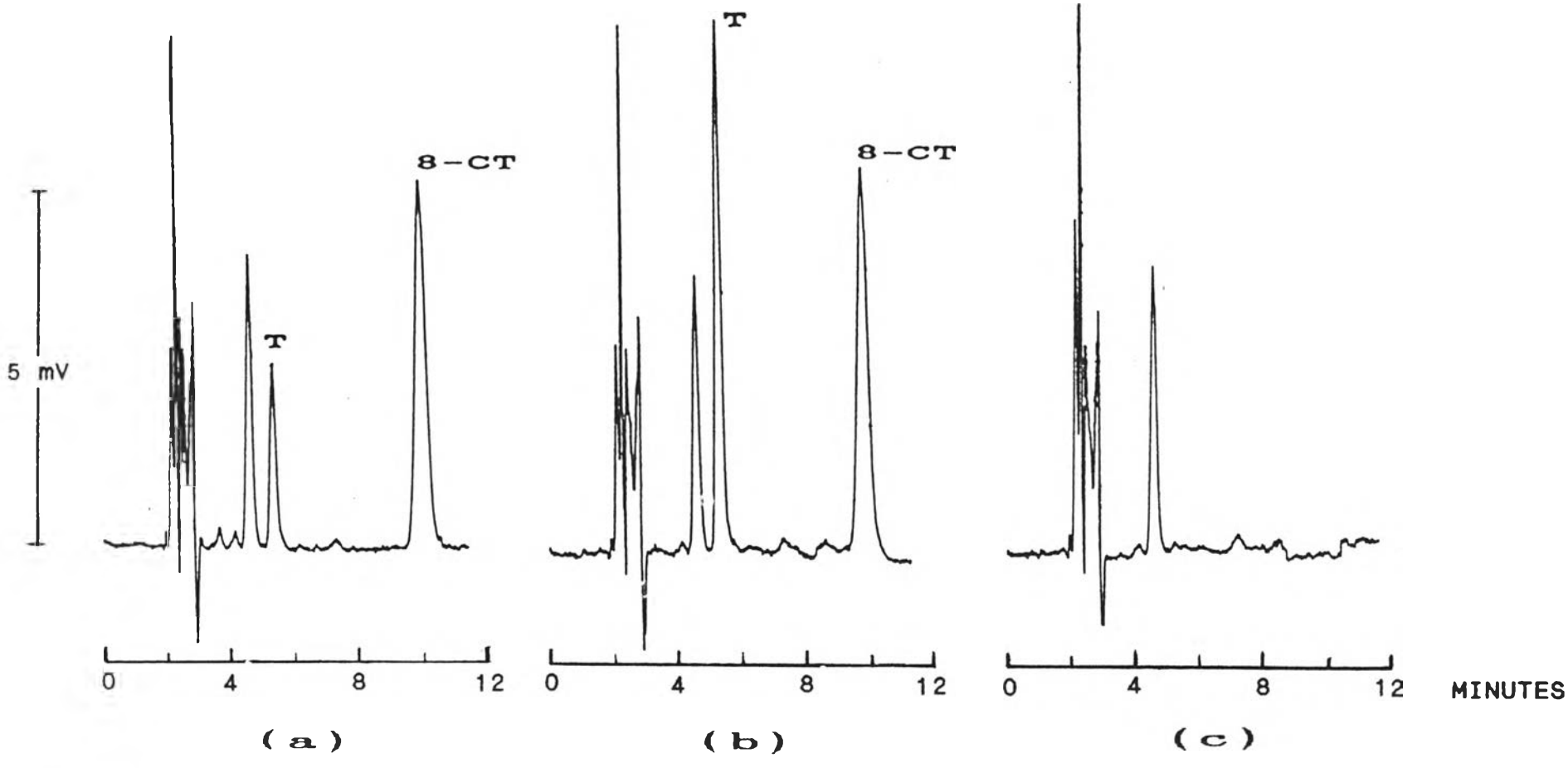

Figure 4. Typical chromatograms of theophylline (T) and 8-chlorotheophylline (8-CT) from (a) a plasma sample and (b) a plasma standard*. Chromatogram (c) was obtained from a human control plasma.

* containing 15 μg/ml of theophylline and 10 μg/ml of 8-chlorotheophylline

were ranged from 0.990 to 0.999. Figure 15 (Appendix C) illustrates a typical standard curve of theophylline concentration. The lower sensitivity limit of theophylline in human plasma was approximately 1.0 mcg/ml.

Based on these results, this analytical method for theophylline in human plasma gave good and reliable results. The coefficient of variation was 3.12% for a 2.5 mcg/ml theophylline plasma standard (n=4).

Plasma Theophylline Level

The individual plasma theophylline concentrations at each appropriate sampling time from 0 to 12 hours for 40 subjects in 4 different groups (i.e., nonsmoking males, nonsmoking females, smoking males and children) are shown in Table 1. The peak plasma level obtained from nonsmoking females was higher than the other 3 groups following administration of the same oral dose of theophylline, 2.4 mg/kg body weight. Peak plasma level in nonsmoking female subjects ranged from 4.9 to 7.0 mcg/ml, whereas in the other groups ranged from 3.8 to 6.4 mcg/ml. At these peak plasma levels, none of the subjects showed any signs of adverse reaction from the drug.

The mean plasma theophylline concentrations from the concentration-time profiles for 4 different groups of subjects are shown in Figure 5, 6, 7, and 8. Each point in the figure is averaged from 10 subjects and the bars represent the standard errors.

Table 1. Individual Plasma Theophylline Concentrations from 40 Subjects in 4 Different Groups after Oral Administration of Theophylline 2.4 mg/kg Body Weight.

GROUP	Time (hr)	Plasma Theophylline Concentration (mcg/ml) subject no. 1	2	3	4	5	6	7	8	9	10	Mean	SEM
A	0.5	5.092	4.637	3.988	4.706	4.036	2.954	3.172	2.871	3.697	3.243	3.840	0.236
	1.0	4.907	4.907	3.748	4.006	4.023	4.218	4.159	4.196	4.415	4.957	4.354	0.129
	1.5	5.496	4.494	3.875	3.535	4.434	4.023	4.349	4.048	4.196	4.537	4.299	0.157
	2.0	5.318	4.793	5.490	3.866	4.572	4.158	4.419	4.329	3.564	3.881	4.439	0.188
	3.0	4.127	3.991	5.127	3.519	3.497	3.608	4.196	3.967	3.712	4.403	4.015	0.149
	4.0	4.404	3.957	4.563	2.980	3.053	3.138	3.569	3.801	3.452	4.012	3.693	0.166
	6.0	4.047	3.564	3.888	2.796	2.568	3.160	3.201	3.173	3.003	2.988	3.239	0.140
	8.0	2.953	2.702	3.235	2.448	2.429	2.767	2.720	3.015	2.775	2.871	2.792	0.074
	10.0	2.659	2.446	2.998	2.300	1.998	2.583	2.097	2.059	2.353	2.020	2.351	0.098
	12.0	2.227	2.062	2.761	1.785	1.675	2.110	1.734	2.182	1.955	1.485	1.998	0.108
B	0.5	2.464	6.122	7.484	4.635	5.033	3.811	2.050	6.123	2.181	3.860	4.376	0.554
	1.0	4.454	5.625	6.577	4.064	6.376	4.528	4.154	5.834	5.181	5.879	5.267	0.277
	1.5	5.015	6.230	6.343	5.510	5.379	4.825	6.146	6.172	4.574	6.225	5.642	0.200
	2.0	4.672	6.109	5.966	5.756	4.926	5.242	5.565	5.606	5.218	6.175	5.523	0.151
	3.0	4.620	5.213	5.602	4.637	4.691	4.181	5.193	5.021	5.038	5.065	4.926	0.120
	4.0	4.346	4.790	4.850	4.430	4.398	4.491	4.649	3.846	4.841	4.991	4.563	0.101
	6.0	3.614	4.223	4.661	3.963	3.476	3.741	3.929	4.155	4.807	4.272	4.084	0.129
	8.0	2.748	3.832	3.966	3.646	3.314	3.585	3.812	3.566	3.668	3.509	3.564	0.102
	10.0	2.572	3.203	3.405	3.135	2.680	3.012	3.165	2.908	3.080	3.215	3.038	0.076
	12.0	2.229	2.555	3.130	2.353	2.164	2.380	2.583	2.482	2.607	3.148	2.563	0.101

A Nonsmoking Males

B Nonsmoking Females

SEM Standard error of the mean

Table 1. Individual Plasma Theophylline Concentrations from 40 Subjects in 4 Different Groups after Oral Administration of Theophylline 2.4 mg/kg Body Weight (cont.).

GROUP	Time (hr)	Plasma Theophylline Concentration (mcg/ml) subject no. 1	2	3	4	5	6	7	8	9	10	Mean	SEM
C	0.5	4.390	4.815	3.894	4.748	5.009	3.226	4.761	3.722	4.431	3.779	4.277	0.177
	1.0	3.929	6.419	4.805	4.730	4.592	4.172	5.354	3.949	3.891	4.705	4.655	0.234
	1.5	3.740	6.418	4.506	5.546	5.814	5.022	5.988	4.155	3.534	4.487	4.921	0.297
	2.0	3.477	5.884	4.211	4.279	4.964	4.230	6.486	3.920	3.319	4.391	4.516	0.301
	3.0	2.970	4.891	3.516	3.615	5.054	3.780	5.148	3.626	3.060	3.869	3.953	0.239
	4.0	2.756	4.207	2.988	3.784	4.531	3.697	4.465	3.215	2.705	3.734	3.608	0.202
	6.0	2.351	4.163	2.454	2.446	3.843	2.979	4.044	2.670	2.398	2.928	3.028	0.216
	8.0	1.688	3.584	2.201	1.861	3.215	2.870	3.315	2.385	1.648	2.455	2.522	0.209
	10.0	1.312	2.779	2.100	1.571	2.479	2.492	2.858	2.101	1.423	1.800	2.091	0.167
	12.0	0.948	2.358	1.601	1.415	2.522	2.170	2.429	1.661	0.917	1.256	1.728	0.182
D	0.5	1.639	3.470	2.924	5.474	4.973	2.525	4.143	6.312	2.967	2.745	3.717	0.442
	1.0	3.469	5.163	4.537	6.478	4.662	4.104	6.015	6.091	4.173	3.388	4.808	0.329
	1.5	4.575	6.029	5.308	6.129	4.624	4.399	5.369	5.113	4.544	4.031	5.012	0.210
	2.0	4.818	5.346	4.872	6.170	4.550	3.063	4.696	4.944	4.440	4.044	4.694	0.242
	3.0	4.031	4.905	4.255	4.955	3.324	2.744	4.120	3.821	3.670	3.558	3.938	0.204
	4.0	3.635	4.463	3.657	4.328	2.806	2.500	3.240	3.347	3.782	3.364	3.512	0.182
	6.0	3.440	4.052	3.403	3.481	2.453	1.760	2.411	2.505	2.567	2.992	2.906	0.205
	8.0	2.423	3.432	3.061	3.324	1.812	1.181	1.686	1.970	2.223	2.266	2.338	0.221
	10.0	2.290	2.971	2.250	2.282	1.472	1.034	1.173	1.433	1.864	1.539	1.831	0.183
	12.0	1.630	2.448	1.692	2.153	0.900	0.709	1.198	1.137	1.110	1.247	1.422	0.166

C Smoking Males

D Children

SEM Standard error of the mean

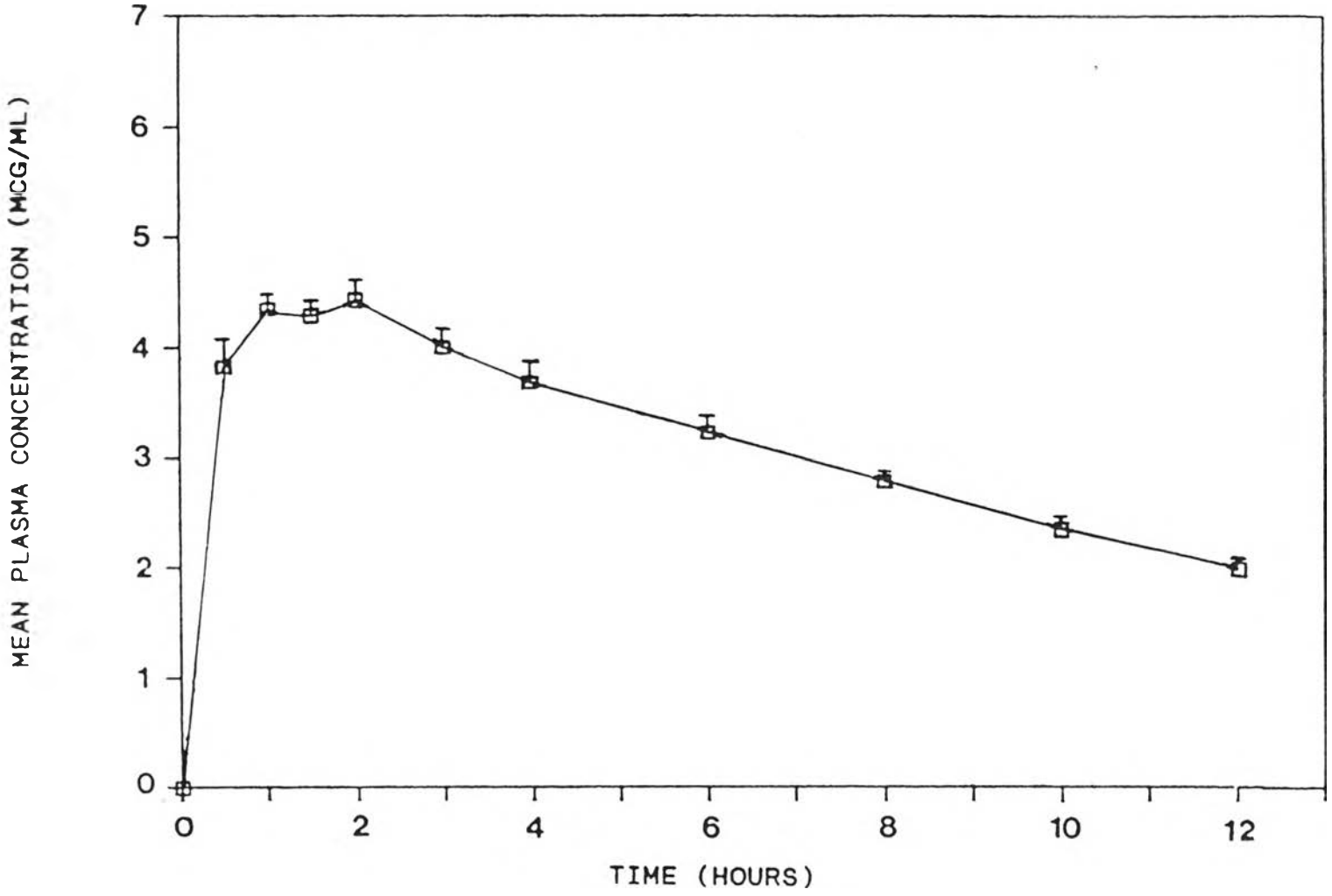

Figure 5. Mean plasma theophylline concentration-time curve from 10 subjects of nonsmoking male group after oral administration of theophylline 2.4 mg/kg body weight

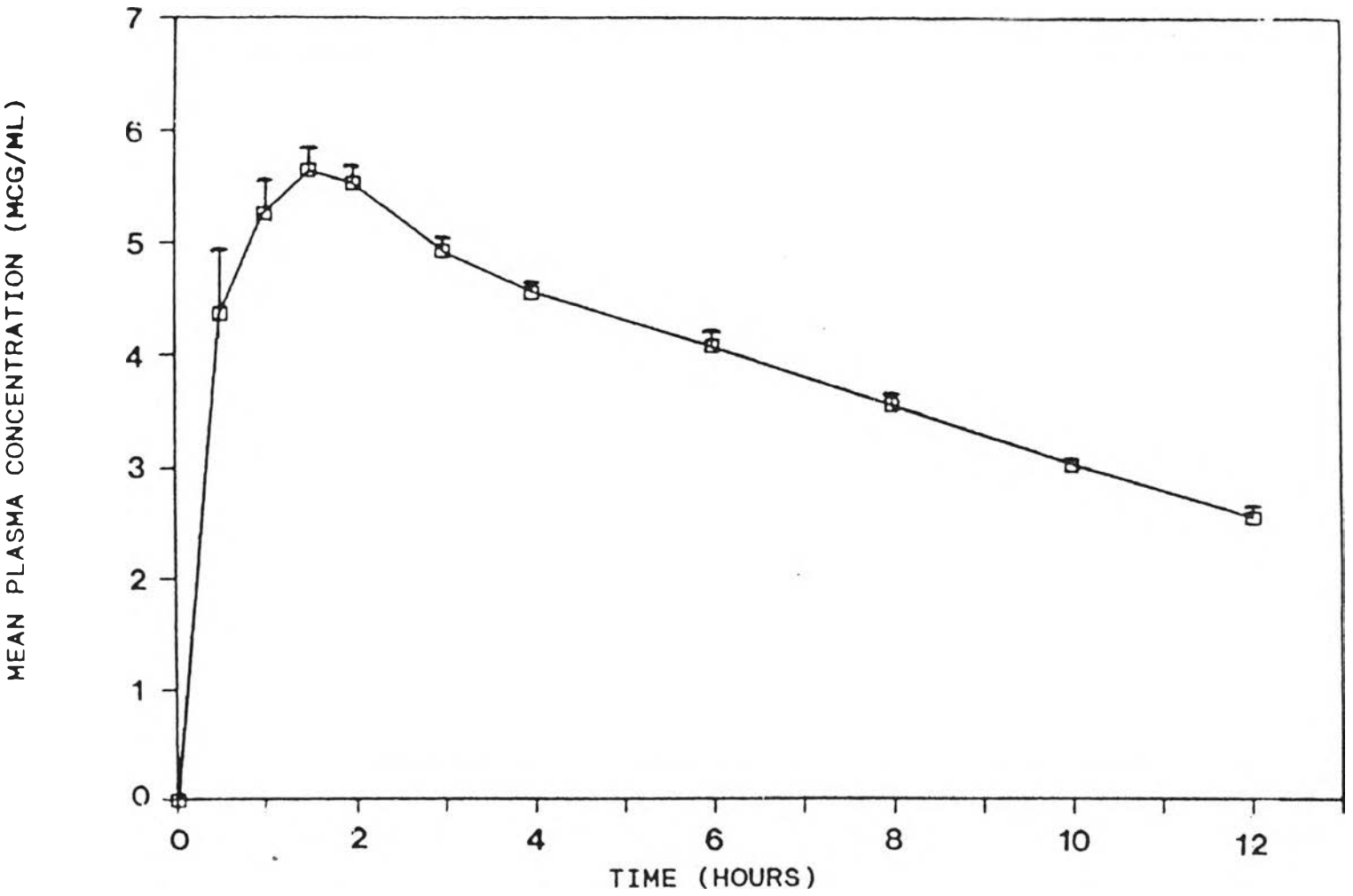

Figure 6. Mean plasma theophylline concentration-time curve from 10 subjects of nonsmoking female group after oral administration of theophylline 2.4 mg/kg body weight

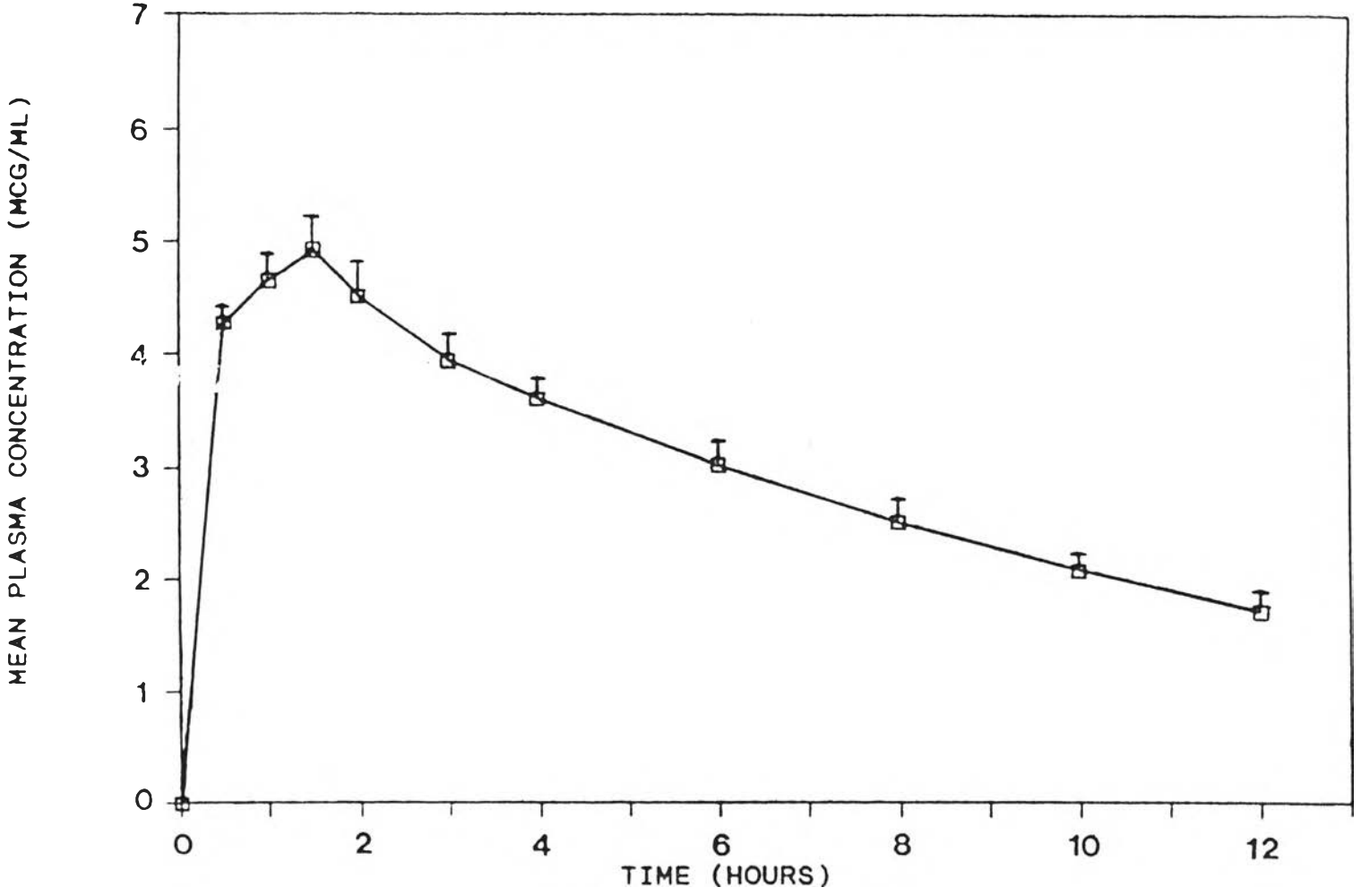

Figure 7. Mean plasma theophylline concentration-time curve from 10 subjects of smoking male group after oral administration of theophylline 2.4 mg/kg body weight

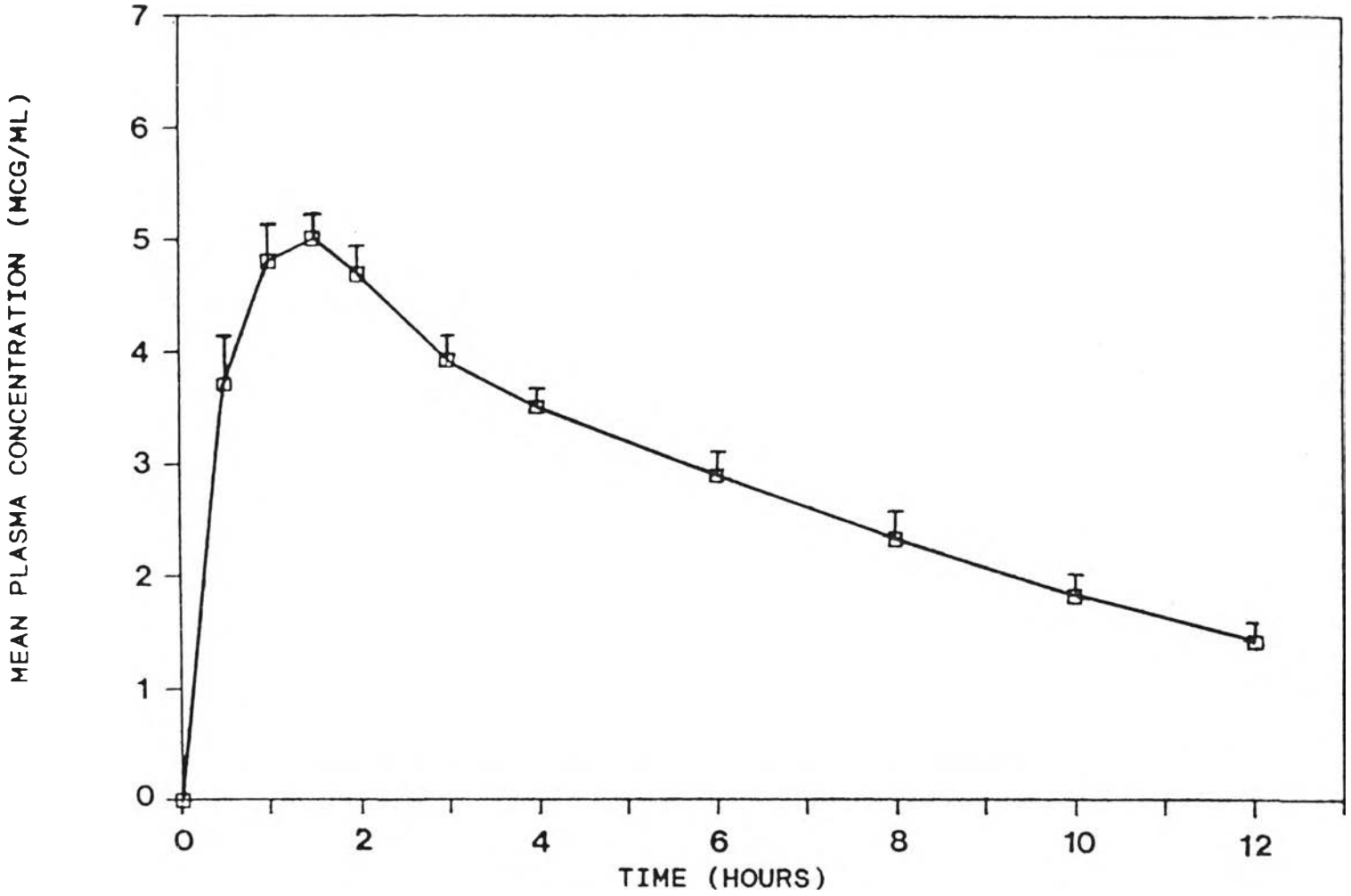

Figure 8. Mean plasma theophylline concentration-time curve from 10 subjects of children group after oral administration of theophylline 2.4 mg/kg body weight

The comparison among the 4 groups of subjects is also summarized in Figure 9. This comparison demonstrates similar curve profiles for all groups of subjects with the rapidly achieving peak plasma concentrations. This implies that theophylline absorption from a syrup dosage form is rather rapid. The average time to reach peak plasma concentration in 4 groups was observed to range from 1.5 to 2.0 hours. The mean peak plasma level in all groups ranged from 4.5 to 5 mcg/ml, except in nonsmoking females which was 5.6 mcg/ml.

Pharmacokinetics of Theophylline

A plot of a log plasma theophylline concentration versus time after an oral dose of 2.4 mg/kg from one subject in nonsmoking male group was used as a representative for all data and shown in Figure 10. In this plot, the decline of plasma concentration with time was monoexponential. A straight line could be drawn through the points of terminal portion, implying that theophylline was eliminated by first-order process. The first order decline was observed in all experiments including our preliminary study of which the sample collection time was extended upto 24 hours. This implied that a one-compartment open model with first-order absorption and first-order elimination could be used for describing the theophylline plasma concentration-time profiles obtained from the experiments.

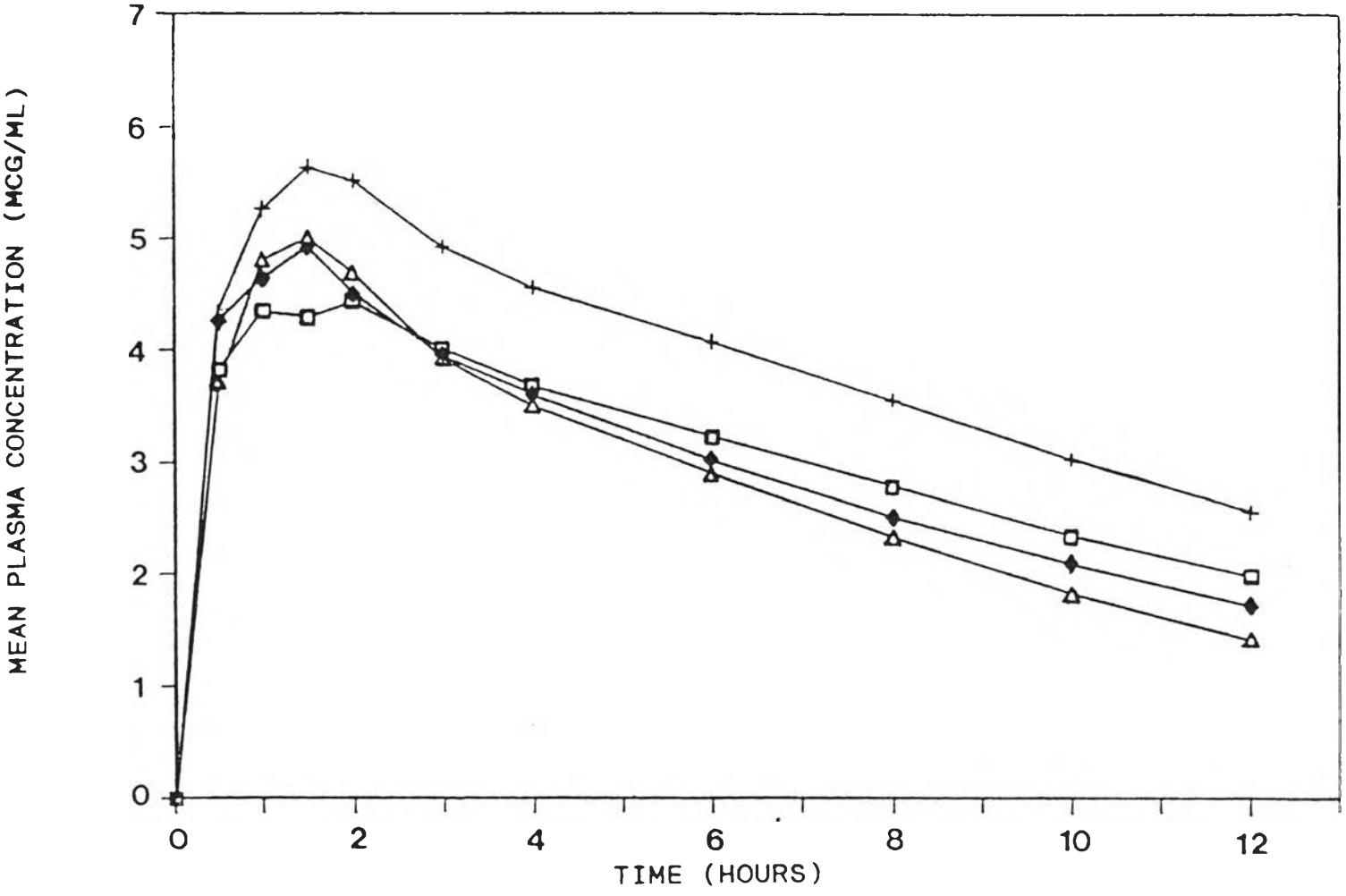

Figure 9. Comparison of mean plasma theophylline concentration-time curve among 4 different groups of nonsmoking male (□—□), nonsmoking female (+—+), smoking male (◆—◆), and children (△—△) after oral administration of theophylline 2.4 mg/kg body weight

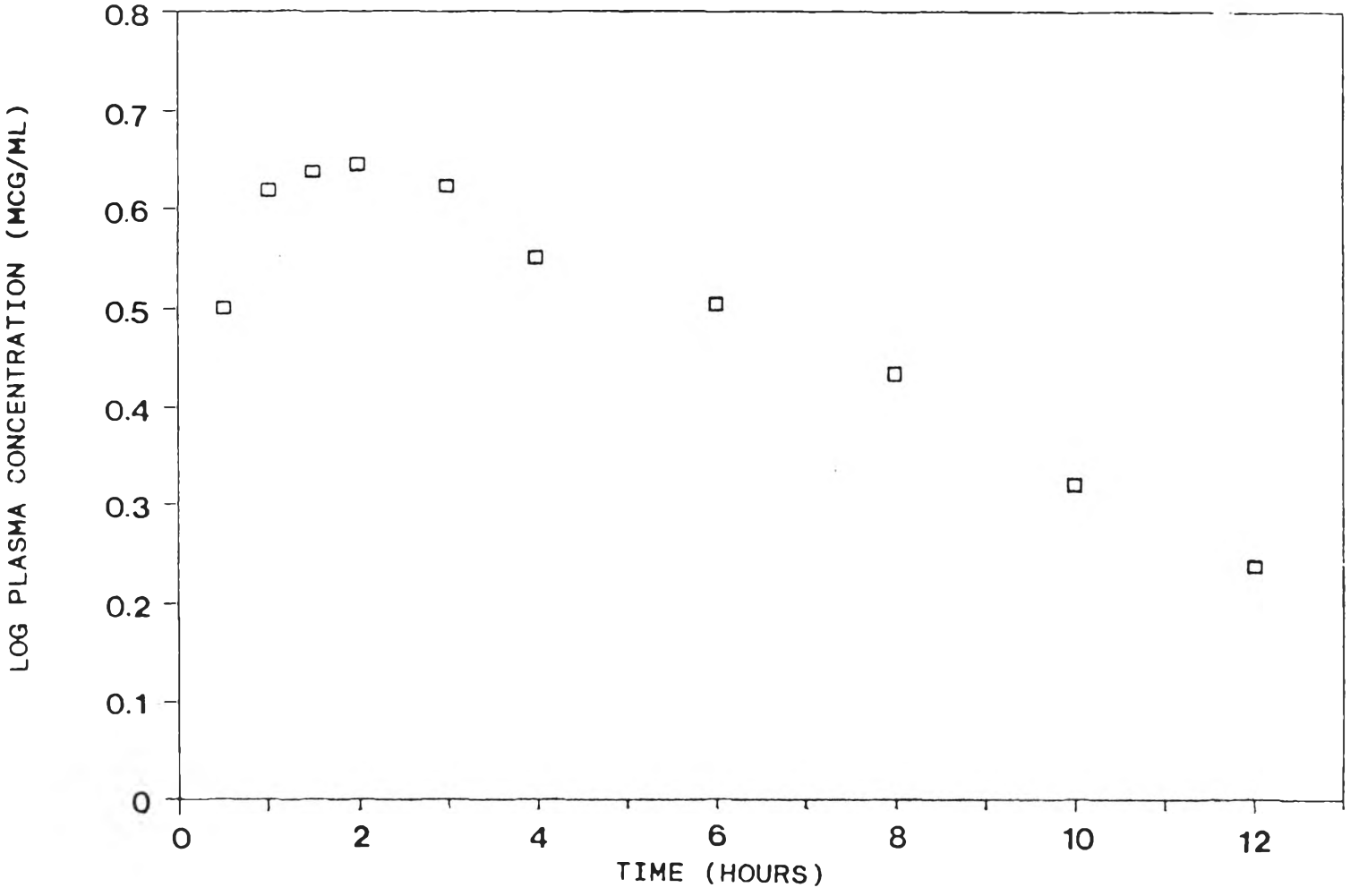

Figure 10. Log plasma theophylline concentration-time profile of subject no.7 from nonsmoking male group after oral administration of theophylline 2.4 mg/kg body weight

Consequently, each data set was fitted to a one-compartment open model with first-order absorption and first-order elimination by nonlinear least-squares regression using the PCNONLIN program. Model 3 was found to fit well to these experimental data sets with good correlation.

The pharmacokinetics of theophylline with oral administration was well described by one-compartment open model with first-order absorption and first-order elimination as shown with a "best fit" line in Figure 11. The best fit line was drawn through the calculated data points obtained by fitting the observed data to the one-compartment model as described previously. The representative log concentration-time profiles from the subjects of nonsmoking males, nonsmoking females, smoking males and children are also presented in Figure 12, 13 and 14, respectively.

The theophylline pharmacokinetic parameters estimated from each data set of 40 subjects for 4 different groups after oral administration of 2.4 mg/kg body weight of theophylline are summarized in Table 2. Each value is averaged from 10 subjects in each group.

The result showed that theophylline in syrup dosage form was absorbed rapidly. This demonstrated by the rather great values of the mean absorption rate constant, K_a , in the 4 groups, which ranged from 4.55 hr^{-1} to 5.73 hr^{-1}. Since the absorption was very fast, the time to peak plasma concentration, t_{max} , was rather short. The mean

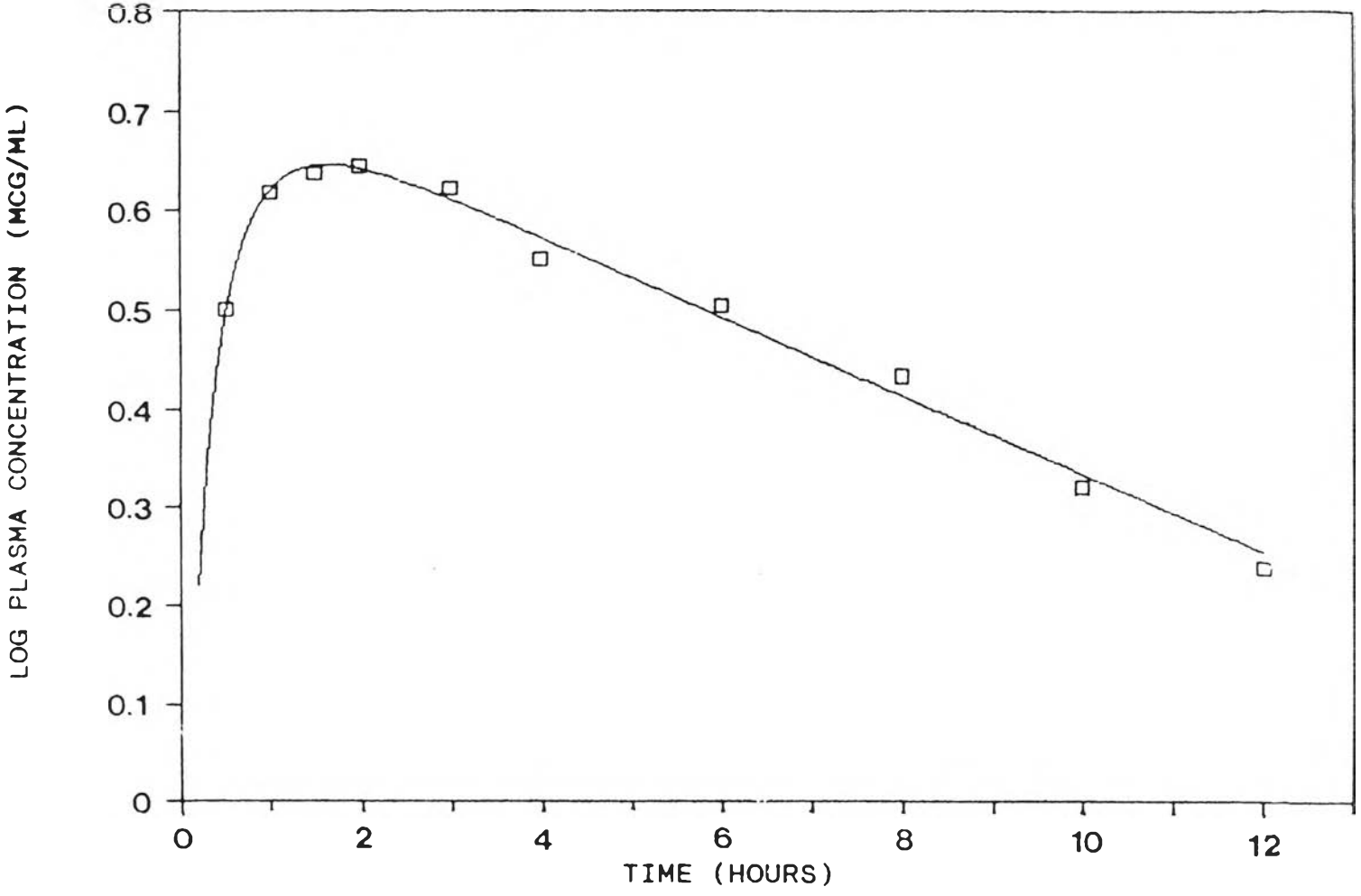

Figure 11. Log plasma theophylline concentration-time profile with the best fit line of subject no.7 from nonsmoking male group after oral administration of theophylline 2.4 mg/kg body weight

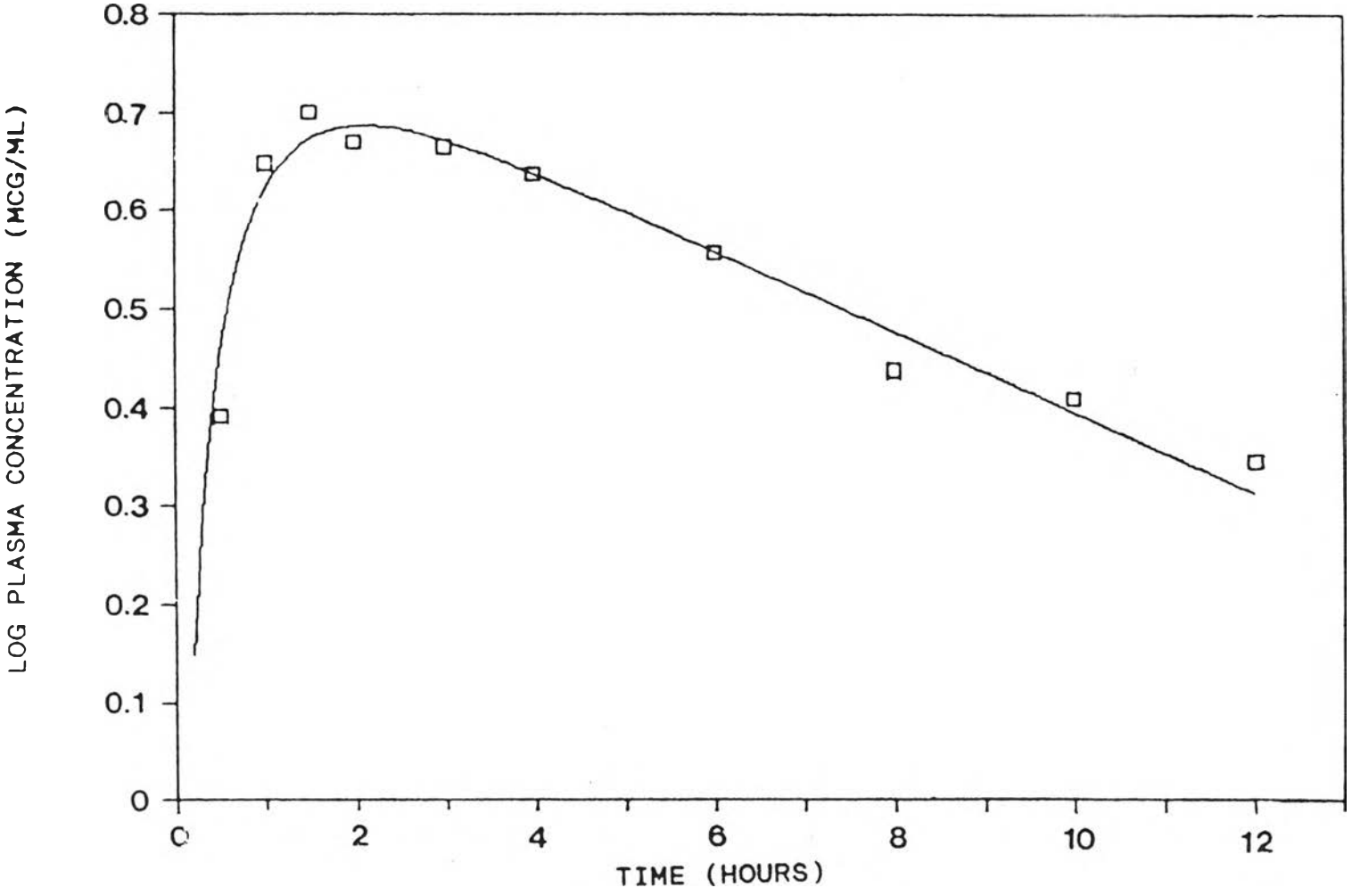

Figure 12. Log plasma theophylline concentration-time profile with the best fit line of a subject from nonsmoking female group after oral administration of theophylline 2.4 mg/kg body weight

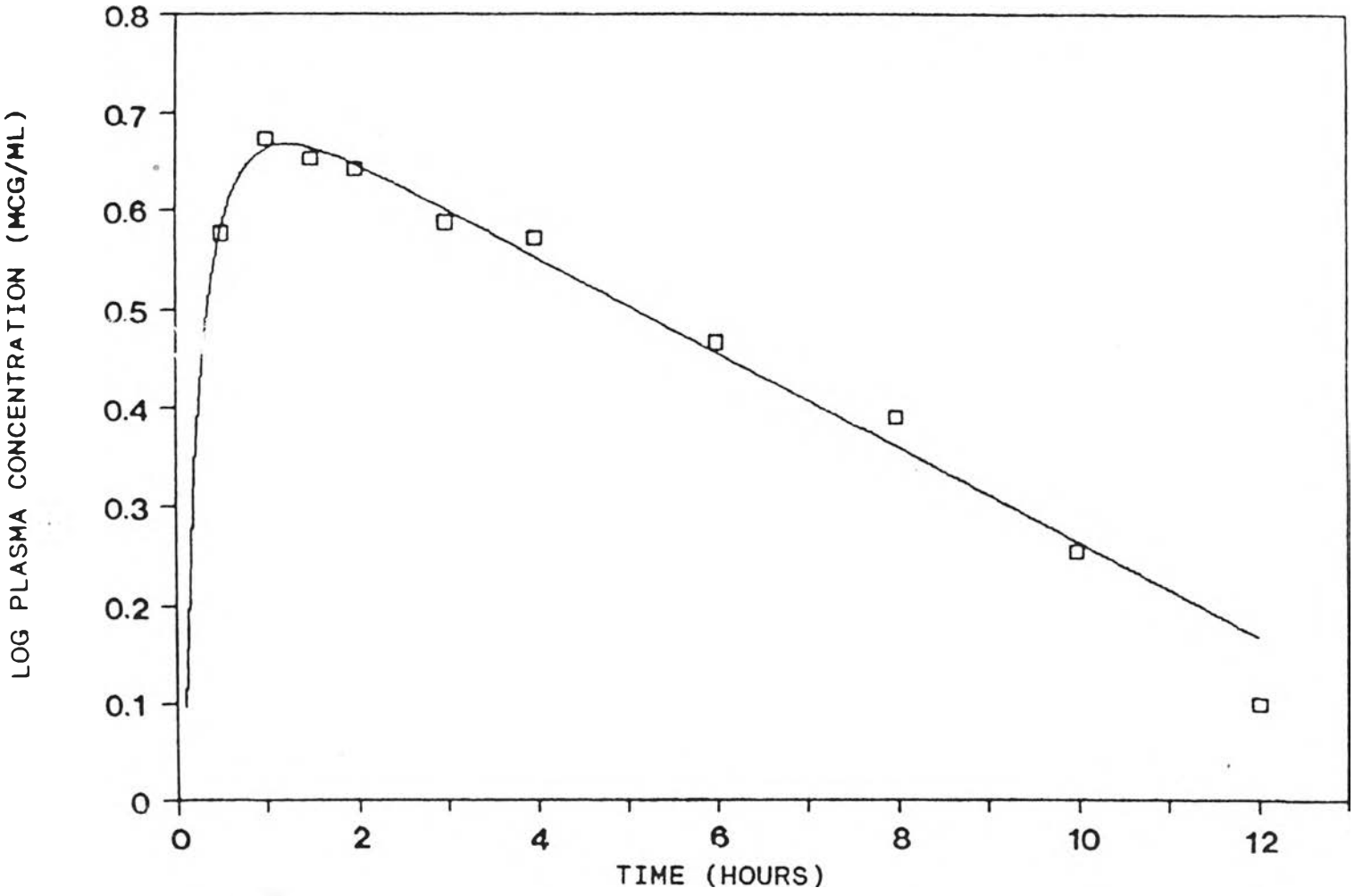

Figure 13. Log plasma theophylline concentration-time profile with the best fit line of a subject from smoking male group after oral administration of theophylline 2.4 mg/kg body weight

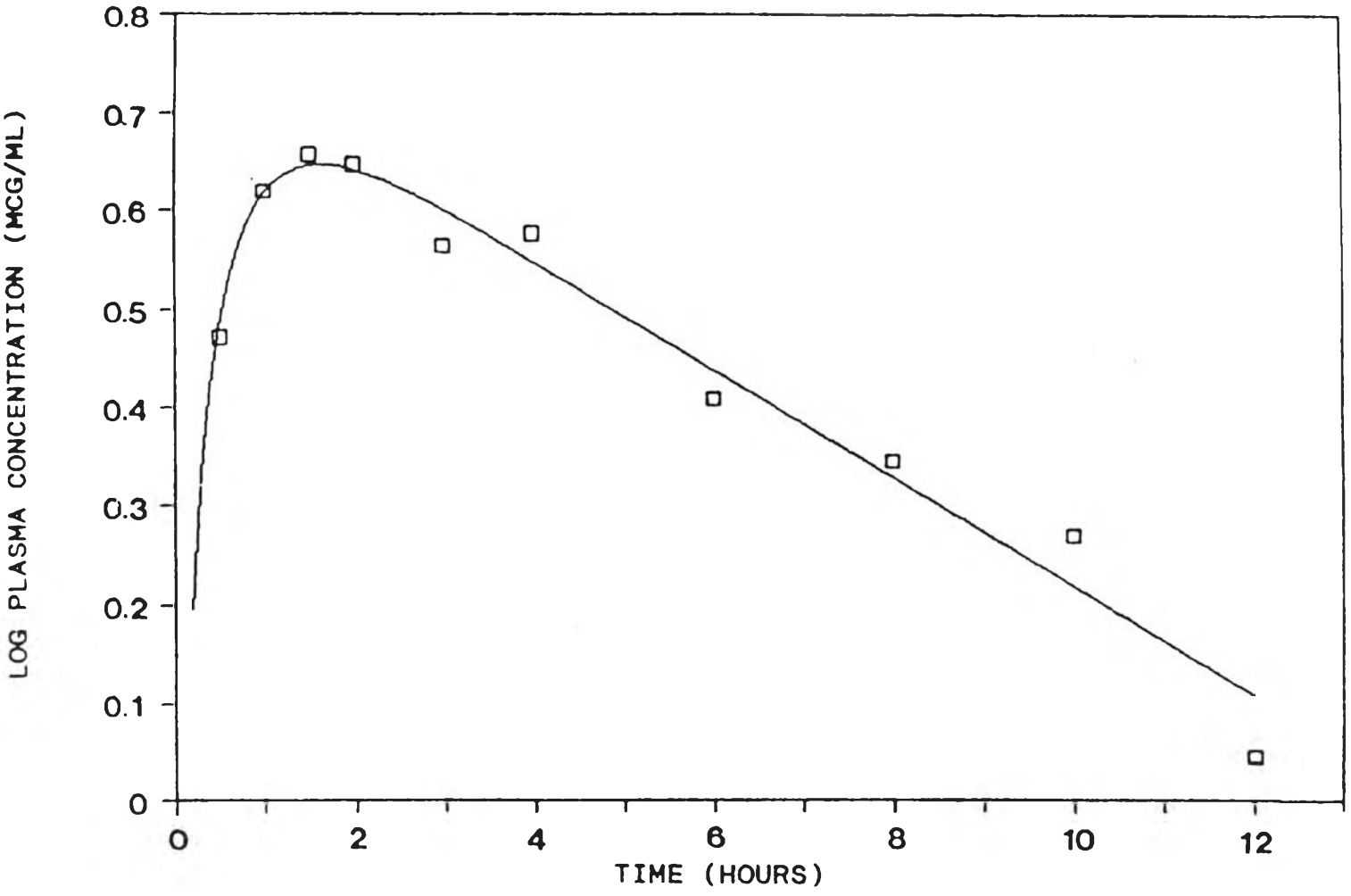

Figure 14. Log plasma theophylline concentration-time profile with the best fit line of a subject from children group after oral administration of theophylline 2.4 mg/kg body weight

Table 2. Pharmacokinetic Parameters of Theophylline in 4 Different Groups After Oral Administration of Theophylline 2.4 mg/kg Body Weight

GROUP	K_a (hr^{-1})	T_{max} (hr)	C_{max} (mcg/ml)	AUC (mcg·hr/ml)	V (L/kg)	K (hr^{-1})	Cl (L/kg/hr)	$t_{1/2}$* (hr)
A	4.55 (1.55)**	1.26 (0.17)	4.53 (0.13)	64.62 (3.16)	0.484 (0.015)	0.0787 (0.0040)	0.038 (0.002)	8.81
B	4.97 (1.86)	1.42 (0.24)	5.67 (0.21)	80.94 (2.96)	0.380 (0.011)	0.0790 (0.0030)	0.030 (0.001)	8.77
C	5.73 (1.75)	1.01 (0.13)	4.87 (0.23)	55.12 (4.89)	0.457 (0.023)	0.1020 (0.0070)	0.047 (0.004)	6.80
D	4.63 (1.81)	1.36 (0.22)	5.02 (0.28)	47.30 (4.42)	0.417 (0.018)	0.1327 (0.0110)	0.056 (0.005)	5.22

A Nonsmoking Males
B Nonsmoking Females
C Smoking Males
D Children
* Harmonic Mean
** Figures in parenthesis are standard eorror of the mean

t_{max} values in the 4 groups ranged from 1.0 to 1.4 hours.

The mean apparent volume of distribution, V , for the 4 groups ranged from 0.38 L/kg to 0.48 L/kg. Nonsmoking females showed the smallest mean V value (0.38 L/kg) which was significantly different from the values obtained from nonsmoking males (0.48 L/kg). The smaller volume implied that the body space for theophylline distribution in this subject group was smaller than those of the others, ie.,the drug resided more in the vascular bed. This was suggested by the significantly larger in the mean AUC and the mean C_{max} values of nonsmoking female group, as presented in Table 2.

Comparisons of Pharmacokinetic Parameters between Nonsmoking Males and the Other Groups

The theophylline pharmacokinetic parameters of nonsmoking males, as a control group, were compared with those of nonsmoking females, smoking males and children, as shown in Table 3, 4 and 5, respectively. The Student's t-test at 5% significant level, was used to determine the statistically significant differences. The effects of sex, smoking status and age on theophylline pharmacokinetics were as follows :

1. Effect of Sex

The mean apparent volume of distribution observed in this study were 0.48 L/kg and 0.38 L/kg in nonsmoking males and nonsmoking females, respectively, as shown in Table 3. The statistics showed a significant difference between them ($p < 0.05$). The smaller volume could reflect the factors of either increased binding of theophylline to plasma protein, or decreased extracellular fluid space (54). The latter was considered to be more possible because the females commonly had a greater accumulation of fat tissue than the males (55). Fat tissue had a smaller proportion of water compared to muscle tissue. Thus, the females had a smaller proportion of total body water to total body weight compared to that of the males (56).

The smaller volume of distribution in nonsmoking female group reflected both significant higher values in AUC and C_{max} than those of nonsmoking male group.

The mean overall elimination rate constant, K, in nonsmoking males and nonsmoking females were almost identical. They were 0.0787 hr^{-1} and 0.0790 hr^{-1} respectively. Furthermore, both groups had a similarly wide variation in K value which ranged from 0.0626 hr^{-1} to 0.0936 hr^{-1}. Mean half-life ($t_{1/2}$), calculated from 0.693/(mean K), in nonsmoking males was very close to that of nonsmoking females. They were 8.81 hr and 8.77 hr,

Table 3. Comparison of Theophylline Pharmacokinetic Parameters between Nonsmoking Males and Nonsmoking Females

GROUP	K_a (hr^{-1})	T_{max} (hr)	C_{max} (mcg/ml)	AUC (mcg·hr/ml)	V (L/kg)	K (hr^{-1})	Cl (L/kg/hr)	t1/2* (hr)
A	4.55 (1.55)**	1.26 (0.17)	4.53 (0.13)	64.62 (3.16)	0.484 (0.015)	0.0787 (0.0040)	0.038 (0.002)	8.81
B	4.97 (1.86)	1.42 (0.24)	5.67 (0.21)	80.94 (2.96)	0.380 (0.011)	0.0790 (0.0030)	0.030 (0.001)	8.77
t-test p value	NS	NS	< 0.0001	0.002	< 0.0001	NS	0.004	

A Nonsmoking Males
B Nonsmoking Females
* Harmonic Mean
** Figures in parenthesis are standard error of the mean
NS Not significant ($p > 0.05$)

respectively. However, the clearance values, Cl , from both groups exhibited a statistically significant difference at significant level of 0.05 ($p = 0.004$). They were 0.038 and 0.030 L/kg/hr in nonsmoking males and nonsmoking females, respectively. The difference in Cl value was resulted from the significant difference in V value, since the clearance parameter, Cl , was calculated from the products of K and V.

In conclusion, sex factor affected some pharmacokinetic parameters of theophylline ,i.e., V, AUC, C_{max}, and Cl. The apparent volume of distribution was shown to be significantly smaller in nonsmoking females than in nonsmoking males with significantly larger in both AUC and C_{max}. The clearance values from both groups were significantly different, whereas no difference in elimination rate constant values was observed.

2. Effect of Smoking

As compared in Table 4, The elimination rate constant (K) was the only parameter that was significantly different between the nonsmoking and smoking males ($p < 0.05$). The mean K value of theophylline in the smoking males was higher than that in the nonsmoking males. In another word, the mean half-life ($t_{1/2}$) of theophylline in the smoking males was shorter than that in the nonsmoking males. The means of K and $t_{1/2}$ in the smoking and nonsmoking males were 0.1020 hr^{-1}, 6.80 hr.

Table 4. Comparison of Theophylline Pharmacokinetic Parameters between Nonsmoking Males and Smoking Males

GROUP	K_a (hr^{-1})	T_{max} (hr)	C_{max} (mcg/ml)	AUC (mcg·hr/ml)	V (L/kg)	K (hr^{-1})	Cl (L/kg/hr)	$t_{1/2}$* (hr)
A	4.55 (1.55)**	1.26 (0.17)	4.53 (0.13)	64.62 (3.16)	0.484 (0.015)	0.0787 (0.0040)	0.038 (0.002)	8.81
C	5.73 (1.75)	1.01 (0.13)	4.87 (0.23)	55.12 (4.89)	0.457 (0.023)	0.1020 (0.0070)	0.047 (0.004)	6.80
t-test p value	NS	NS	NS	NS	NS	0.014	NS	

A Nonsmoking Males
C Smoking Males
* Harmonic Mean
** Figures in parenthesis are standard error of the mean
NS Not significant ($p > 0.05$)

and 0.0787 hr^{-1}, 8.77 hr., respectively. The mean clearance value, Cl, in the smoking males (0.047 L/kg/hr) tended to be higher than that in nonsmoking males (0.038 L/kg/hr). However, there was no difference between them at the significance level tested.

In conclusion, this study demonstrated that cigarette smoking increased theophylline elimination rate constant and decreased the elimination half-life in Thai subjects. The total body clearance also tended to be higher for smokers than nonsmokers. Based on these results, it was indicated that cigarette smoking had a tendency to induce theophylline metabolism, since hepatic metabolism appeared to be the major route of theophylline elimination (47,48). Grygiel and Birkitt (19) found that cigarette smoking induced both theophylline metabolism pathways, N-demethylation and 8-hydroxylation. Induction of hepatic microsomal enzymes may be the probable mechanism of enhanced biotransformation of theophylline in cigarette smokers. Since the polycyclic aromatic hydrocarbons (PAHs), primary causal agents in cigarette smoke, have been shown to increase the activity of hepatic microsomal enzymes, especially aryl hydrocarbon hydroxylase (AHH) (57,58). Kapitulnik et al (59) also found strong correlations between AHH activity and the rates of metabolism of several drugs.

Many previous studies conducted in other countries clearly demonstrated that cigarette smoking induced the metabolism of theophylline as reflected by

both significantly increased total body clearance and elimination rate constant with decreased elimination half-life (15-19). However, the non-significantly increasing of total body clearance in Thai smokers as observed from this study may be influenced by some factors such as a difference in race and a variability in the cigarette compositions. These factors may lead to a less induction of theophylline metabolism in Thais than in Caucasians.

3. Effect of Age

As shown in Table 5, the mean theophylline elimination rate constant and total body clearance were both significantly higher in children as compared to those of nonsmoking male adults. More variability of these parameters among subjects were found in children group (boys, aged in range of 7 to 12 years). The mean values of K, Cl and $t_{1/2}$ in children group were 0.1320 hr^{-1}, 0.056 L/kg/hr, and 5.22 hr, respectively. The mean values of V and AUC were significantly larger in adults (0.0484 L/kg, 64.6 mg·hr/L) than in children (0.0417 L/kg, 47.3 mg·hr/L)

From these results, both increasing theophylline elimination rate constant and total body clearance with decreasing elimination half-life in children group, indicated that children eliminated theophylline more rapidly than adults. In another word, the rate of theophylline metabolism in children was faster

Table 5. Comparison of Theophylline Pharmacokinetic Parameters between Nonsmoking Male Adults and Children

GROUP	K_a (hr^{-1})	T_{max} (hr)	C_{max} (mcg/ml)	AUC (mcg·hr/ml)	V (L/kg)	K (hr^{-1})	Cl (L/kg/hr)	$t_{1/2}$* (hr)
A	4.55 (1.55)**	1.26 (0.17)	4.53 (0.13)	64.62 (3.16)	0.484 (0.015)	0.0787 (0.0040)	0.038 (0.002)	8.81
D	4.63 (1.81)	1.36 (0.22)	5.02 (0.28)	47.30 (4.42)	0.417 (0.018)	0.1327 (0.0110)	0.056 (0.005)	5.22
t-test p value	NS	NS	NS	0.010	0.022	< 0.0001	0.012	

A Nonsmoking males
D Children
* Harmonic Mean
** Figures in parenthesis are standard error of the mean
NS Not significant ($p > 0.05$)

than adults and seemed likely to decrease as one grows older. This was supported by many previous investigations (11-14).

Comparisons of Theophylline Pharmacokinetic Parameters between the Present Study and the Other Investigations

As shown in Table 6, the comparisons were classified into 3 groups of healthy nonsmokers, healthy smokers, and children. In all 3 groups, the mean apparent volume of distribution values among several investigations were similar, whereas there were a great variation in the mean clearance and elimination half-life values.

The mean apparent volume of distribution value was ranged from 0.4 to 0.5 L/kg for adults in both nonsmokers and smokers and approximately 0.4 L/kg for children. In all 3 groups, the mean clearance values of the present study seemed to be lower than those of the other investigations which were conducted in other countries, with the longer elimination half-life. The reason for this difference results may probably due to the difference in race. Thais may have a lower theophylline metabolism than Caucasians. This was supported by the study of Tuchinda et al. (25,26) which have suggested that the theophylline clearance in Thai children was slower than that in Caucasian children, as evidence by the longer elimination half-life (ranged from approximately 7 to 17 hours) as listed in Table 6.

Table 6. Comparisons of Theophylline Pharmacokinetic Parameters from the Present Study and the Other Investigations

Population	No.Subj /sex	Age (Yr)	Parameter V (L/kg)	Parameter Cl (L/kg/hr)	Parameter $t_{1/2}$ (hr)	Authors (Ref.No.)
HEALTHY NONSMOKERS						
	10 /M[a]	23-38	0.484±0.015	0.038±0.002	8.81	Present Study
	10 /F[a]	22-34	0.380±0.011	0.030±0.001	8.77	Present Study
	6 /M[b]	24-57	0.231±0.080	0.114±0.050	11.02	Chrzanowski (40)
	9 /M[b]	19-31	0.318±0.161	0.075±0.019	4.39	Mitenko & Ogilvie (41)
	3 /M[b]	22-30	0.429±0.026	0.067±0.022	4.40	Mitenko & Ogilvie (42)
	6 /M[b]	22-27	0.448	0.057	5.80	Ellis (11)
	14 /M[b]				7.2±1.8	Jenne (15)
	8 (3/F,5/M)[a]	24-32	0.38 ±0.04		7.0±1.7	Hunt (16)
	15(9/F,6/M)[a]	20-32	0.474±0.077	0.040±0.008	8.23	Powell (17)
	19(8/F,11/M)[a]	22-35	0.415±0.083	0.052±0.021	8.1±2.4	Jusko (18)
	8 (4/F,4/M)[a]			0.032±0.002		Grygiel (19)
HEALTHY SMOKERS						
	10 /M[a]	21-33	0.457±0.023	0.047±0.004	6.80	Present Study
	10 /M[b]				4.1±1.2	Jenne (15)
	8 (6/F,2/M)[a]	21-52	0.50 ±0.12		4.3±1.4	Hunt (16)
	7 (3/F,4/M)[a]	22-31	0.498±0.059	0.063±0.019	5.35	Powell (17)
	24(19/F,5/M)[a]	20-47	0.496±0.071	0.075±0.031	5.7±2.1	Jusko (18)
	9 (5/F,4/M)[a]			0.053±0.006		Grygiel (19)

a Oral Administration
b Intravenous Administration

Table 6. Comparisons of Theophylline Pharmacokinetic Parameters from the Present Study and the Other Investigations (cont.)

Population	No.Subj /sex	Age (Yr)	Parameter V (L/kg)	Parameter Cl (L/kg/hr)	Parameter $t_{1/2}$ (hr)	Authors (Ref.No.)
CHILDREN						
	10 / M[a,c]	7-12	0.417±0.018	0.056±0.005	3.8-7.9(5.22)	Present Study
	10(5/F,5/M)[a,d]	8-13			9-17	Tuchinda (25)
	20 /F,M[b,d]	9-13			6.8-10.8	Tuchinda (26)
	27 /F,M[b,e]	1-9		0.093		Zaske (13)
	6 (3/F,3/M)[b,e]	4-10		0.073±0.019		Weinberger (14)
	17 /F,M[b,e]	4-12		0.090±0.024		Ginchansky (12)
	30 /F,M[b,e]	6-17	0.422	0.087		Ellis (11)
	32 /F,M[b,e]	10-18		0.077		Zaske (13)

a Oral Administration
b Intravenous Administration
c Thai healthy children
d Thai asthmatic children
e Non-Thai asthmatic children