Korea J. of Toxicology
Vol. 4, No. 1, pp. 1-12, 1988

EFFECT OF SMOKING ON THEOPHYLLINE PHARMACOKINETICS IN NORMAL KOREAN VOLUNTEERS

Kyoung Ho Park, Hyun Teak Shin, and Nak Doo Kim*

Department of Pharmacy, Seoul National University Hospital, Seoul 110, Korea.
**College of Pharmacy, Seoul National University, Seoul 151, Korea.*

ABSTRACT: *In order to evaluate the effect of cigarette smoking on the pharmacokinetics of theophylline in Koreans, doses of 4.5 to 5.0 mg/kg of theophylline, as injectable aminophylline, were administered to 12 normal young volunteers (male, 22 to 35 yrs; mean, 26 yrs) through intravenous infusion over 30 minutes, and pharmacokinetics of theophylline were tested. Among subjects, six were nonsmokers and the other were smokers (range 1 to 2 packs/day). Also the correlations between plasma and saliva theophylline concentrations were investigated by determining the concentrations of theophylline in saliva simultaneously at each plasma sampling time.*

The total body clearances of theophylline in smokers (Mean ± SD, 0.0578 ± 0.0092 L/hr/kg) were appreciably higher than those of nonsmokers (Mean ± SD, 0.0359 ± 0.0063 L/hr/kg), and the half-lives of theophylline in smokers averaged 5.36 ± 1.22 hr, and significantly shorter than those of nonsmokers which averaged 9.14 ± 1.73 hrs($p < 0.005$). But the apparent volumes of distribution of theophylline did not show any significant difference between smokers (Mean ± SD, 0.44 ± 0.05 L/kg) and nonsmokers (Mean ± SD, 0.46 ± 0.05 L/kg).

The average concentration ratios in saliva and plasma were 0.61 in smokers and 0.56 in nonsmokers after 2 hrs following drug administrations, and the smoker group had a slightly higher value of ratio(S/P) than the nonsmoker group ($p < 0.05$).

The correlations between saliva and plasma theophylline concentration in smokers were $r = 0.852$($p < 0.0005$) within 2 hr and $r = 0.985$($p < 0.0005$) after 2 hrs and also those of nonsmokers were $r = 0.729$($p < 0.0005$) within 2 hrs and $r = 0.957$ ($p < 0.0005$) after 2 hrs starting the infusion.

From the results, it was found that smoking cigarettes had significantly increased the clearance of theophylline and that the relationships between saliva and plasma theophylline concentrations in all subjects were better after 2 hrs than within 2 hrs starting the infusion of aminophylline.

Keywords: *Pharmacokinetics, theophylline, saliva concentration, human volunteers, aminophylline, smoking cigarette, metabolism, clearance.*

INTRODUCTION

Theophylline is commonly used as bronchodilator in the treatment of asthma patients and also used extensively in the management of apnea in premature infants(1). The effective therapeutic plasma levels of theophylline are 8-20 μg/ml(2) and concentrations above these ranges frequently induce toxic effects(3-4).

In adults, theophylline is extensively metabolized to 3-methylxanthine (13-35%), 1-methyluric acid(15-19%) and 1,3-dimethyluric acid(35-40%) and less than 10% of the administered dose is eliminated as unchanged by renal excretion (5-7). The metabolism of theophylline can be affected by several host factors such as age, sex, genetic constitution, diet, smoking and drinking habits, as well as the functional capacity of various organs critical in drug absorption, distribution and elimination(8-10).

Previous studies have shown that cigarette smoking may influence the clinical efficacy and toxicity of some drugs such as benzodiazepine, propoxyphene, and chloropromazine(11-13). Also rapid metabolism of theophylline in smokers has been postulated(10).

Because theophylline has a narrow range of therapeutic plasma concentration, but the disposition rates could vary widely according to individual characteristics and biotransformation rates(14-16). Therefore, it is important to evaluate the pharmacokinetic characteristics of theophylline in Korean people for optimal medications of this drug.

Then, the purpose of present investigation is to examine the effects of cigarette smoking on the pharmacokinetics of theophylline in normal Korean volunteers, and also to evaluate the correlations between plasma and saliva concentrations of theophylline in smoking and nonsmoking groups.

MATERIALS AND METHODS

1. Human volunteers

Twelve normal young subjects were divided into two groups, smoker and nonsmokder. The subjects in smoker group were six male volunteers who smokded at least one pack of cigarette per day and their ages ranged from 22 to 31 yr(mean, 26yr), and those of nonsmoker group were also six male volunteers who ranged in age from 22 to 35yr (mean, 26yr).

Physical examinations by physician and serum biochemical measurements were performed prior to entry into this study and all showed normal ranges(Table 1.).

For 3 days prior to and during this study, all subjects have refrained from ingesting any food or beverages containing caffeine or theobromine.

Table 1. Description of the volunteer's informations and clinical laboratory tests

Subject	Age (yr)	Height (cm)	Weight (Kg)	SGOT (0-25IU/l)*	SGPT (0-29IU/l)	BUN (0-26mg/ml)	S.Cr. (0.7-0.9mg/dl)
SMOKER							
K.S.	27	168	63	21	19	18.3	0.9
S.K.	24	167	68	45	45	13.9	0.7
J.M.	31	172	53	37	26	15.6	0.7
K.H.	29	170	72	19	24	12.8	1.2
H.W.	25	172	70	33	38	12.2	0.4
S.M.	25	167	63	3	8	19.8	0.9
NONSMOKER							
K.J.	35	174	62.5	7	28	12.7	0.9
G.S.	22	184	82	17	8	18.7	0.8
K.K.	23	168	54	44	26	13.3	0.7
B.H.	25	165	63	30	26	6.5	0.7
S.G.	26	179	68	17	14	11.4	1.2
H.H.	27	176	65	10	8	19.8	0.9

*The values in parenthesis mean the normal range of each serum biochemical test.

2. Chemical reagents and instruments

Theophylline and β-hydroxyethyltheophylline were obtained from Sigma. Injectable aminophylline (Dae Won Pharm. Co., 250mg/5ml) were used as the test drug. Other reagents, such as chloroform, isoamylalcohol, and acetonitrile used for the analysis of theophylline by liquid chromatograph were of HPLC or Guranteed grade.

The liquid chromatograph used for the analysis of theophylline in biological fluids was Hewlett Packard Model 1090 high performance liquid chromatograph equipped with Model 3392 integrator(Hewlett Packard) and Model 8513 microcomputer(Hewlett Packard).

3. Drug administrations and specimen sampling

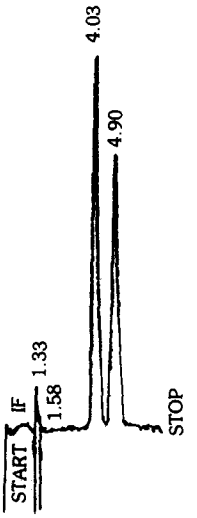
Each subjects were given a dose of 4.5 to 5.0 mg/kg of theophylline as aminophylline diluted with 50 ml of saline through intravenous infusion over 30 minutes. All smokers were permitted to smoke during the study.

Blood and saliva specimens were collected from each subject before and 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24hr after starting the infusion of aminophylline. Saliva specimens were taken by stimulating saliva flow with citric acid (100 to 200mg) at 2 min. before each plasma sampling time, and after sampling salivas, all sujects gargled their mouths with tap water. The heparin-locked syringes were used for sampling bloods. All plasma and saliva specimens were stored frozen at -70°C until analysis of theophylline.

Two subjects among nonsmoker group showed toxic effects (drowsiness and headache) but they were recovered to normal state after 2 hours.

4. The determination of theophylline in plasma and saliva by HPLC

Theophylline concentrations in plasma and saliva were measured by using a high



The assay of theophylline in plasma and saliva
Method : Extraction by organic solvent
Column: RP-18,200 × 4.6mm
Solvent : 10mM sodium acetate buffer pH 4.0: Acetonitrile (91:9, v/v)
Detector: U.V. 280nm
Flow rate: 2.0ml/min
Chart speed: 0.3cm/min

Fig. 1. The chromatogram is of theophylline and β-hydroxy ethyl theophylline (i.s.) by HPLC.
Retention time:
4.03min. is theophylline (10ug/ml)
4.90min. is β-hydroxy theophylline

performance liquid chromatograph (Hewlett Packard Model 1090 liquid chromatograph) equipped with a ODS column(4.6 × 20cm, Hewlett Packard). The mobile phase was 9% acetonitrile made up in 10mM sodium acetate buffer(pH 4.0), the pressure was 120 bar, and the U.V. detector was set at 280 nm.

200 ul of plasma and 1 ml of saliva were taken in 10 ml of capped test tubes, and β-hydroxyethyltheophylline disolved in methanol was added as the internal standard. These were extracted with 7 ml of chloroform containing 5% isopropylalcohol after voltexing for 1 min and centrifugation at 3000 rpm for 5 min. The upper layer was aspirated and lower layer was transferred to another clean test tube. The organic solvent was evaporated by purging with nitrogen gas in the 60°C water bath. Then, the residues were reconstituted by adding 0.1 ml of methanol, and about 25 ul of sample was injected onto the column.

This analytical method was not affected by the metabolites of theophylline, caffeine and theobromine. The chromatograms of theophylline and β-hydroxyethyltheophylline were shown at Fig. 1.

5. Analysis of pharmacokinetic parameters and statistics

The data were fitted to appropriate pharmacokinetic equations using nonlinear least square regression analysis using the MULTI program in a personal computer. Half-life, apparent volume of distribution and total body clearance were evaluated by the computer program. The differences of pharmacokinetic characteristics of theophylline between smoker and nonsmoker group were tested by using student t-test.

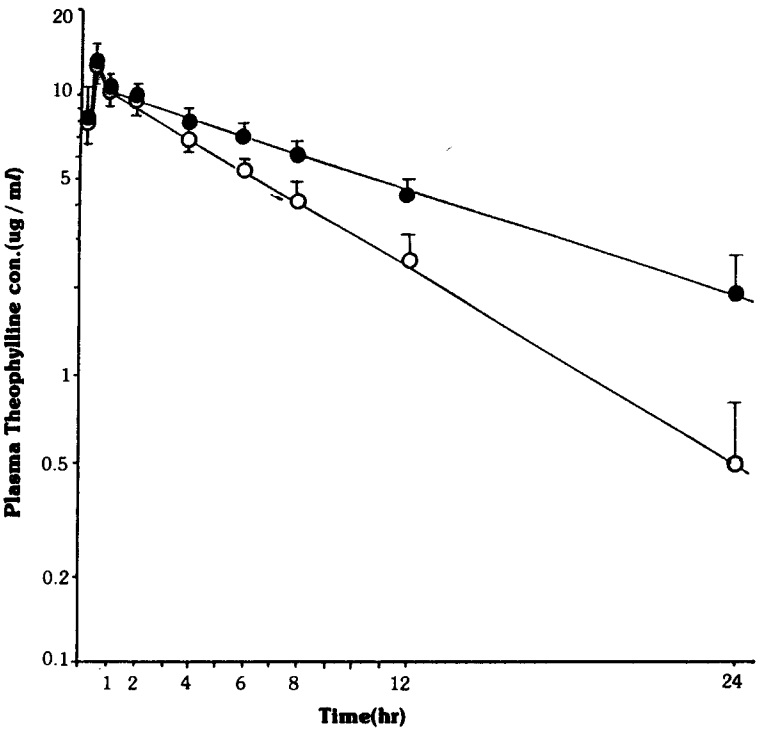


Fig. 2. Plasma theophylline concentrations in normal volunteers after intravenous infusions of Aminophylline. All theophylline concentrations of subjects were normalized to dose of 5mg/Kg of theophylline.
○—○ : Smoker(n = 6) ●—● : Nonsmoker(n = 6)

RESULTS

1. Comparison of pharmacokinetic parameters of theophylline between smokers and nonsmokers.

Average plasma theophylline concentrations of smokers (n = 6) and nonsmokers (n = 6) were plotted as a function of time in Fig. 2. From the plasma concentration-time curves, the pharmacokinetic parameters were calculated by fitting data at one exponential equations using personal computer program, MULTI. The area under the plasma vs time curves(AUC) was obtained by a model dependent intergration to allow for the calculation of the apparent volume of distribution(Vd) and total body clearance (CLt). A summary of pharmacokinetic parameters of theophylline in smokers and nonsmokers are shown in Table 2. Also the statistical comparisons of pharmacokinetic parameters between two groups and average values of each parameter of all subjects are listed in Table 3.

The mean half-life in smokers was 5.36(SD = 1.22) hr and the value was significantly shorter($p < 0.005$) than that of 9.14(SD = 1.73) hr found in nonsmokers. Also mean total body clearance of theophylline in smokers was 0.0578 (SD = 0.0092) L/hr/kg, significantly higher ($p < 0.005$) than that of 0.359 (SD = 0.0063) L/hr/kg found in nonsmokers. But the difference of the apparent volumes of distribution of

Table 2. Summary of individual volunteer's pharmacokinetic parameter of theophylline following intravenous infusion of aminophylline for 30 min.

SUBJECT	DOSE (mg/Kg)	Ke (hr^{-1})	$t_{1/2}$ (hr)	AUC (ug·hr/ml)	CLt (L/hr/Kg)	Vd (L/Kg)	Ratio of Con.(S/P)**
AMOKER*							
K.S.	4.72	0.1657	4.18	65.13	0.0725	0.44	0.617
S.K.	5.00	0.1318	5.26	87.56	0.0571	0.43	0.598
J.M.	4.81	0.1122	6.18	89.97	0.0535	0.48	0.537
K.H.	4.43	0.0954	7.27	98.80	0.0448	0.47	0.585
H.W.	4.55	0.1707	4.06	80.16	0.0568	0.33	0.690
S.M.	4.72	0.1336	5.18	76.41	0.0618	0.46	0.630
MEAN	4.71	0.1349	5.36	83.01	0.0578	0.44	0.610
SD	0.20	0.0294	1.22	11.75	0.0092	0.05	0.050
NONSMOKER							
K.J.	4.76	0.0624	11.10	186.90	0.0255	0.41	0.578
G.S.	4.67	0.0838	8.27	119.72	0.0390	0.47	0.582
K.K.	4.72	0.1085	6.39	112.14	0.0421	0.39	0.492
B.H.	4.72	0.0786	8.82	114.35	0.0413	0.53	0.552
S.G.	5.00	0.0644	10.76	155.26	0.0322	0.50	0.590
H.H.	4.90	0.0729	9.51	139.80	0.0351	0.48	0.580
MEAN	4.80	0.0784	9.14	138.03	0.0359	0.46	0.562
SD	0.13	0.0168	1.73	29.17	0.0063	0.05	0.037

* Smoker: 1-2 packs of cigarettes a day

** The ratio of saliva concentration of theophylline to plasma concentration was evaluated after 2hrs following intravenous infusion for 30 min.

Table 3. The comparison of pharmacokinetic parameters of theophylline between smoker and nonsmoker.

	SMOKER (n = 6)	NONSMOKER (n = 6)	ALL SUBJECTS (n = 12)
Ke (hr^{-1})	0.1349 ± 0.0294 (1.72)*	0.0784 ± 0.0168	0.1067 ± 0.0373
t1/2 (hr)	5.36 ± 1.22 (0.59)	9.14 ± 1.73	7.25 ± 2.44
AUC (ug·hr/ml)	83.01 ± 11.75 (0.60)	128.03 ± 29.17	110.52 ± 35.71
CLt (L/hr/Kg)	0.0578 ± 0.0092 (0.61)	0.0359 ± 0.0063	0.0468 ± 0.0137
Vd (L/Kg)	0.44 ± 0.05 (0.96)	0.46 ± 0.05	0.45 ± 0.05
Ratio of Con.(S/P)	0.610 ± 0.050 (1.09)	0.562 ± 0.037	0.586 ± 0.049

* The parenthesis indicates the ratio of parameter of smoker to that of nonsmoker

**$P<0.05$ ***$P<0.005$ ****$P<0.0005$

theophylline between two groups was not significant.

The ratios of saliva to plasma theophylline concentrations averaged 0.61 (SD = 0.05) in smokers, slightly higher ($p < 0.05$) than the value of 0.56 (SD = 0.037) found

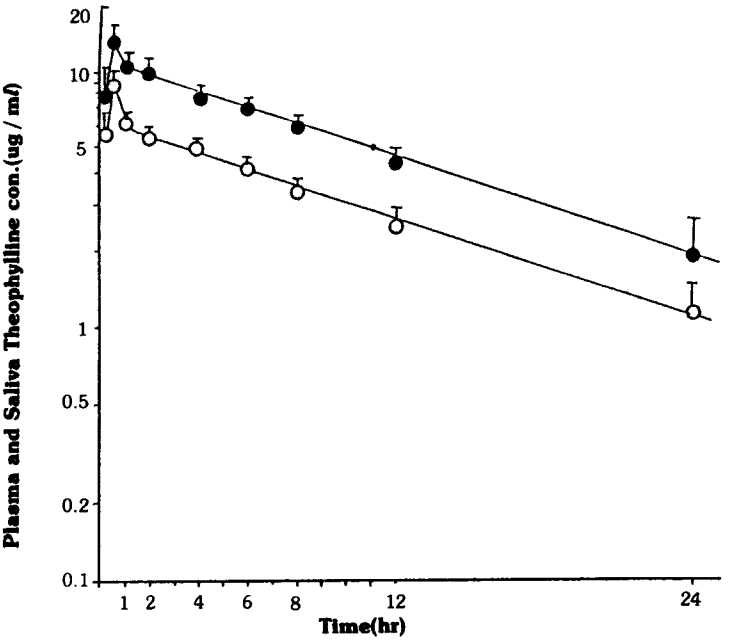


Fig. 3. Plasma and saliva theophylline concentrations in normal nonsmokers after intravenous infusion of Aminophylline. All theophylline concentrations of subjects were normalized to dose of 5mg/Kg of theophylline. Results were expressed as mean of six nonsmokers with S.D.
●—● : Plasma ○—○ : Saliva

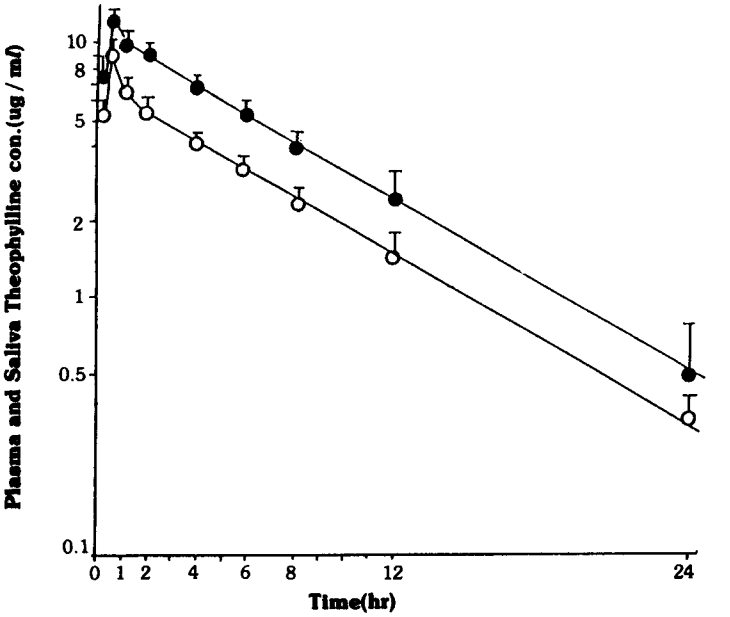


Fig. 4. Plasma and saliva theophylline concentrations in normal smokers after intravenous infusion of Aminophylline. All theophylline concentrations of subjects were normalized to dose of 5mg/Kg of theophylline. Results were expressed as mean of six smokers with S.D.
●—● : Plasma ○—○ : Saliva

Table 4. Summary of individual pharmacokinetic parameters of theophylline from saliva theophylline concentration-time curves following intravenous infusion of aminophylline for 30min.

SUJECT	Ke (hr^{-1})	t1/2 (hr)	AUC (ug·hr/ml)	CLt (L/hr/Kg)	Vd (L/Kg)
SMOKER					
K.S.	0.1583	4.38	39.79	0.1188	0.75
S.K.	0.1330	5.21	50.92	0.0982	0.74
J.M.	0.1155	6.00	47.33	0.1017	0.88
K.H.	0.1324	5.23	50.13	0.0833	0.67
H.W.	0.1353	5.12	53.10	0.0858	0.63
S.M.	0.1350	5.13	44.09	0.1071	0.79
MEAN	0.1349	5.18	47.56	0.1000	0.74
SD	0.0137	0.51	4.92	0.0122	0.09
NONSMOKER					
K.J.	0.0738	9.39	99.27	0.0480	0.65
G.S.	0.0714	9.66	75.11	0.0621	0.87
K.K.	0.1165	5.95	55.42	0.0852	0.73
B.H.	0.0808	8.58	68.20	0.0692	0.86
S.G.	0.0573	12.09	97.44	0.0513	0.89
H.H.	0.0715	9.70	79.56	0.0616	0.86
MEAN	0.0785	9.23	78.67	0.0625	0.81
SD	0.0200	1.99	16.35	0.0134	0.10

in nonsmokers. The averaged apparent volume of distribution and the ratio of saliva to plasma theophylline concentrations in all subjects were 0.45, 0.05 L/kg and 0.586 ± 0.049, respectively.

2. Plasma and saliva concentrations in nonsmokers and smokers

The mean plasma and saliva theophylline concentrations of nonsmokers and smokers were plotted as a function of time in Fig. 3 and Fig. 4, and a summary of individual subject's pharmacokinetic parameter calculated from saliva curves is shown in Table 4.

The mean half lives of the drug in saliva in nonsmokers and smokers were 8.82 (SD = 2.25) hr and 5.14 (SD = 0.52) hr, and they were similar to the mean values of 8.87 (SD = 1.90) hr and 5.14 (SD = 1.12) obtained from plasma curves, respectively. The half-life of salivary theophylline in each subject has correlated well with that of plasma half life.

The mean total body clearance and the mean volume of distribution calculated from the saliva curves were 0.0625 (SD = 0.0134) L/hr/kg and 0.81 (SD = 0.10) L/kg in nonsmokers, and 0.1000 (SD = 0.0122) L/hr/kg and 0.74 (SD = 0.09) L/Kg in smokers, respectively. The values of total body clearance and volume of distribution in all subjects obtained from saliva curves were higher than those obtained from plasma curves.

3. Correlations between plasma and saliva concentrations

The ratios of saliva to plasma concentrations after 2 hr following the infusion of

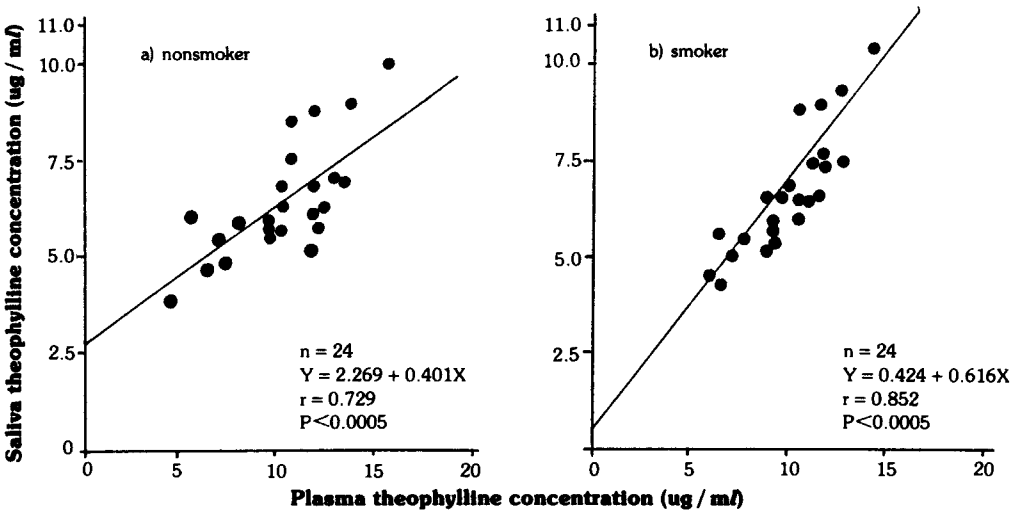


Fig. 5. Correlation between plasma and saliva theophylline concentrations in normal volunteers within 2hr after intravenous infusion of aminophylline for 30min.

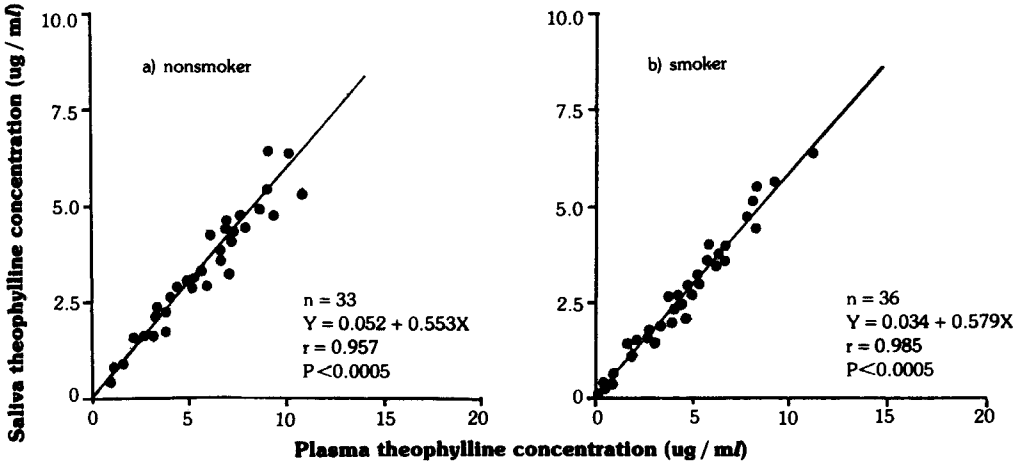


Fig. 6. Correlation between plasma and saliva theophylline concentration in normal volunteers over 2hr to 24hr after intravenous infusion of Aminophylline for 30min.

theophylline in smokers and nonsmokers are shown in Table 2. The scatter-grams of saliva and plasma theophylline concentrations are shown in Fig. 5 and Fig. 6, and have been used to evaluate the correlations of two parameters in smokers and non-smokers,

The correlation curves within 2 hr were represented by Y(saliva con.) = 2.269 ± 0.410X (plasma con.) ($r = 0.729$, $p < 0.0005$) for the nonsmokers and Y = 0.424 ± 0.610X ($r = 0.852$, $p < 0.0005$) for the smokers. Also, those after 2 hr were represented by Y = 0.052 ± 0.553X ($r = 0.957$, $p < 0.0005$) for the nonsmokers and Y = 0.035 ± 0.579X ($r = 0.985$, $p < 0.0005$) for the smokers, respectively. The correlations of two parameters obtained after 2 hrs were better than those obtained within 2

hrs starting the infusion of aminophylline.

DISCUSSION

We have investigated the pharmacokinetics of theophylline in the normal young Korean volunteers and the relationships between the saliva and plasma theophylline concentrations as well as the effects of smoking cigarettes on the rates of clearance of theophylline in human.

The data obtained from our study on the effects of smoking on the pharmacokinetics of theophylline were similar to the values reported in other studies (26) and the rates of clearances of theophylline in smokers were higher than those in nonsmokers.

About 90% of the administered theophylline in the body are eliminated mainly by metabolism in the liver and less than 10% of the administered doses are excreted as unchanged parent drug by urine. Thus, the increased clearance of theophylline in smokers may be explained by the enzyme inductions in the liver.

The theophylline clearance may be decreased by a number of factors, including congestive heart failure, cirrhosis, β-blocking agents, macrolide antibiotics, cimetidine and large doses of allopurinol (17-19). In addition, various factors such as cigarette and marijuana smoking, charcoal-broiled meat, phenytoin and possibly phenobarbital may increase the rate of theophylline clearance (20-22).

The stimulating effects of smoking cigarettes on the liver microsomal metabolizing enzymes which causes a more rapid biotransformation of the drug was also reported in earlier studies with pentazocin and phenacetin (23-24).

Cigarette smoke contains many chemical materials, among them, the bezo[a]pyrene and polycyclic hydrocarbons are considered as the enzyme inducers. Hunt and coworkers (25) showed that there were good correlations between body clearances of theophylline and the serum concentrations of thiocyanate in smokers ($r = 0.785$, $p < 0.001$).

In the same report, Hunt *et al.* also found that the apparent volume of distribution of theophylline averaged 0.50 ± 0.12 L/kg in smokers and 0.38 ± 0.04 L/kg in nonsmokers, and they accounted for these phenomena by the well known effects of cigarette smoking and peripheral vasoconstrictions. The latter factor may alter the distributions of theophylline by inhibiting the return of theophylline from body tissue. But from our study, the apparent volumes of distribution were not different between two groups; apparent volumes of distribution of smokers and nonsmokers averaged 0.45 ± 0.05 L/kg and 0.46 ± 0.05 L/kg, respectively.

However, the volume of distributions of theophylline obtained from our volunteers were not significantly different from those reported for the Americans (calculated from lean body weights (mean, 0.5 L/kg)).

The half-lives of theophylline obtained in our study were also similar to the values of pharmacokinetic parameters found in American population(26).

We have also investigated the relationships of saliva and plasma theophylline concentration, in order to evaluate the possibility of estimating plasma theophylline concentrations from saliva. Good correlations between plasma and saliva theophylline concentrations were obtained for both smokers and nonsmokers. Since the free drug in blood can penetrate the cell membrane and quickly transferred to saliva, if the ratios

of saliva to plasma concentrations are constant, saliva concentrations can be used to monitor the drug concentrations instead of measuring plasma concentrations.

In our study, the correlations between saliva and plasma theophylline concentrations obtained after 2 hr were better than those obtained within 2 hrs starting the drug administration for both smokers and nonsmokers. These phenomena were considered that the ratios of saliva to plasma theophylline concentrations are more variable in distributional phase of drugs to body tissues rather than during the eliminational phase.

From the results of our study, it was found that the smokers must be administered higher doses of theophylline or with shorter intervals of dosing regimens because of increased clearance. The best way of dosing theophylline is to apply the pharmacokinetics interpretations of plasma concentrations. Our study suggests that the use of saliva theophylline concentrations for the dosing regimens may be recommendable instead of plasma concentrations after recognizing the ratios of saliva to plasma theophylline concentrations.

ACKNOWLEDGEMENTS

This work was supported by the special clinical research grant of Seoul National University Hospital (1986).

REFERENCES

1. Aranda, J.V. and Turman, T.: Methylxanthine in apnea of prematurity. Clin. Perinatol 6, 87 (1976).
2. Koup, J.R., Schentag, J.J. and Vance, J.W.: Biopharmaceutics and pharmacokinetics. *Am. J. Hospi. Pharm.* 38, 949 (1976).
3. Hendeles, L. and Weinbereger, M.: Avoidance of adverse effects during chronic theraphy with theophylline. *Drug. Intell. Clin. Pharmacol.* 14, 522 (1980).
4. Orivie, R.I.: Clinical pharmacokinetics of theophylline. *Clin. Pharmacokinet.* 3, 267 (1978).
5. Desiraju, R.K. and Sugita, E.T.: *J. Chromatogr. Sci.* 15, 563 (1977).
6. Brodie, B.B., Axelrod, J. and Reichenthal, J.: *J. Biol. Chem.* 194, 215 (1952).
7. Jenne, J.W., Nagasawa, H.T. and Thompson, R.D.: *Clin. Pharmacol. Ther.* 19, 375 (1976).
8. Jusko, W.J., Schentag, J.J., Clark, J.H., Gardner, M. and Yurchak, A.M.: Enchanced biotransformation of theophylline in marijuna and tobacco smokers. *Clin. Pharmacol. Ther.* 24, 406 (1978).
9. Grygiel, J.J. and Birkett, D.J.: Cigarette smoking and theophylline clearance and metabolism. *Clin. Pharmacol. Ther.* 30, 491 (1981).
10. Jusko, W.J., Gardner, M.J., Mangione, A., Schentag, J.J., Koup, J.R. and Vance, J.W.: Factors affecting theophylline clearance: age, tabacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, barbiturates and ethanol. *J. Pharm. Sci.* 68, 1358 (1979).
11. Boston Collaborative Drug Surveillance Program: Clinical depression of the central nervous system due to diazepam and chlorodiazepoxide in relation to cigarette smoking and age. *N. Engl. J. Med.* 288, 277 (1973).

12. Boston Collaborative Drug Surveillance Program: Decreased clinical efficacy of propoxyphene in cigarette smokings. *Clin. Pharmacol. Ther.* 14, 259 (1973).
13. Boston Collaborative Drug Surveillance Program: Drowsiness due to chlorpromazine in relation to cigarette smoking. *Arch. Gen. Psychiatry.* 31, 211 (1974).
14. Ogilvie, R.I.: Clinical pharmacokinetics of theophylline. *Clin. Pharmacokinet.* 3, 267 (1978).
15. Mitenko, P.A., and Ogilvie, R.I.: Pharmacokinetics of intravenous theophylline. *Clin. Pharmacol. Ther.* 14, 509 (1973).
16. Cornish, H.H., and Christman, A.A.: The metabolism of theobromine, theophylline and caffein in man. *J. Biol. Chem.* 228, 315 (1957).
17. Roberts, P.K., Grice, T., Wood, L., Petroff, V., and McGuffie, C.: Cimetidine impairs the elimination of theophylline and antipyrine. Gastroenterol. 81, 19 (1981).
18. Manfredi, R.L., and Vessell, E.S.: Inhibition of theophylline metabolism by long-term allopurinol administration. *Clin. Pharmacol. Ther.* 29, 224 (1981)
19. Renton, K.W., Gray, T.D., and Hung, O.R.: Depression of theophylline eliminations by erythromycin. *Clin. Pharmacol. Ther.* 30, 422 (1981).
20. Marquis, J., Carruthers, S.G., Spence, J.D., Brownstone, Y.S., and Toogood, J.H.: Phenytointheophylline interaction. *N. Engl. J. Med.* 307, 1189 (1982).
21. Piafsky, K.M., Sitar, D.S., and Ogilvie, R.I.: Effect of phenobarbital on the disposition of intravenous theophylline. *Clin. Pharmacol. Ther.* 22, 336 (1977).
22. Kappas, A., Alvares, A.P. and Anderson, K.E.: Effect of charcoal-broiled beef on antipyrine and theophylline metabolism. *Clin. Pharmacol. Ther.* 23, 445 (1978).
23. Keeri-Szanto, M., and Pomeroy, J.R.: Atmospheric pollution and pentazocin metabolism. Lancet 1, 947 (1971).
24. Pantuck, E.J. and Hsiao, K.C.: Effect of cigarette smoking on Phenacetin metabolism. *Clin. Pharmacol. Ther.* 15, 9 (1974).
25. Hunt, S.H., Jusko, W.J., and Yurchak, A.M.: Effect of smoking on theophylline disposition. *Clin. Pharmacol. Ther.* 19, 546 (1976).
26. Winter, M.E.: Basic Clinical Pharmacokinetics. San Francisco: Applied the Therapeutics, Inc., 125 (1980).