Effect of smoking on theophylline disposition

The pharmacokinetics of theophylline were examined in a group of nonsmokers and in heavy smokers (1 to 2 packs/day) before and 3 to 4 mo after cessation of cigarette smoking. The half-life of theophylline in smokers averaged 4.3 (SD = 1.4) hr, significantly shorter than the mean value in nonsmokers (7.0, SD = 1.7 hr). The apparent volume of distribution of theophylline was somewhat larger in smokers (0.50 ± 0.12 L/kg) than in nonsmokers (0.38 ± 0.04 L/kg). The body clearance of theophylline was appreciably larger and relatively more variable in smokers (100 ± 44 ml/min/1.73 m²) than in nonsmokers (45 ± 13 ml/min/1.73 m²). Serum concentrations of thiocyanate, a biotransformation product of cyanide which is inhaled with smoke, were used to monitor the smoking status of the subjects. The body clearances of theophylline showed a good correlation ($r = 0.785$, $p < 0.001$) with the serum thiocyanate concentrations. Of the 8 smokers, only 4 managed to refrain from smoking for at least 3 mo, and these subjects showed no significant change in theophylline elimination. The increase in theophylline clearance caused by smoking is probably the result of induction of drug-metabolizing enzymes that do not readily normalize after cessation of smoking.

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Approximately one third of the adult population in the United States smokes cigarettes. It is important, therefore, to determine whether smoking alters the pharmacologic effects or the pharmacokinetics of drugs that have a low therapeutic index. Recent studies have shown that the clinical efficacy and toxicity of benzodiazepines,[2] propoxyphene,[3] and chlorpromazine[4] may be influenced by cigarette smoking. More rapid metabolism of these drugs in smokers has been postulated. Direct evidence for an increased rate of biotransformation of drugs in smokers has been found with pentazocine[11] and phenacetin.[19]

Patients with lung disease often have a history of cigarette smoking and may require theophylline. This drug has a narrow therapeutic serum concentration range of 10 to 20 mg/L,[9, 17] a wide range of disposition rates in typical patients,[9] and is largely eliminated by biotransformation. We examined the role of cigarette smoking in determining the phar-

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macokinetics of theophylline, including the effect of cessation of smoking and the utility of serum thiocyanate concentrations as an index of cigarette consumption.

Methods

Eight normal adult subjects (6 F, 2 M) who smoked at least one pack of cigarettes per day (range 1 to 2 packs/day) over the previous year participated in the study. The volunteers ranged in age from 21 to 52 yr (mean, 28). The control subjects (3 F, 5 M) consisted of a similar group of adults who ranged in age from 24 to 32 yr (mean, 27) and who had either never smoked or had not smoked for at least the two previous years. No subjects had a past illness or received medications (except oral contraceptives in 1 nonsmoker and in 2 smokers, and estrogens in 1 smoker) which might affect liver function. The smokers tended to drink more coffee or tea (mean: 5.0, SD = 3.1 cups/day) than the nonsmokers (mean: 3.3, SD = 1.6 cups/day). Data for 3 of the subjects were obtained from an earlier study by Koysooko, Ellis, and Levy.[13] Serum biochemical measurements (SMA 6 and 12) were within the normal range for all subjects.

All subjects refrained from ingesting any food or beverages containing caffeine or theobromine for 24 hr prior to and during the study. Other drugs, except for oral contraceptives, were similarly avoided for at least 3 days.

Each subject received an oral dose of 3 to 5 mg/kg of theophylline as aminophylline (Searle) in 50 to 100 ml of water or orange juice in the morning. Three subjects had eaten a light breakfast more than 1 hr earlier; the other subjects were fasted. Blood and saliva specimens were collected from each subject at frequent intervals before and for 8 to 16 hr after the dose of theophylline. Saliva flow was stimulated by allowing the subjects to chew on a small piece of plastic film (Parafilm). Five of the subjects were restudied 3 to 4 mo after the cessation of smoking. Three of the nonsmokers were also studied on two occasions.

Theophylline concentrations in biologic samples were measured by high-performance liquid chromatography using a DuPont Model 830 Liquid Chromatograph (Wilmington) with a

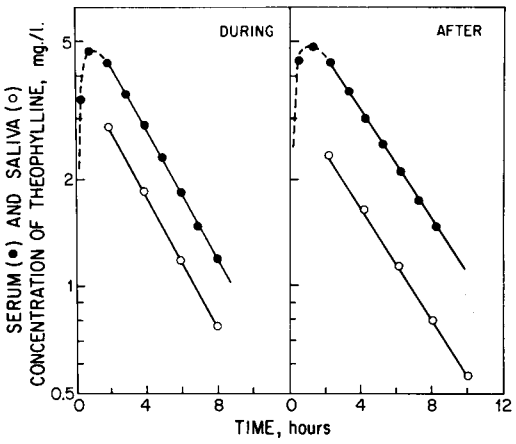

Fig. 1. Time-course of absorption and elimination of theophylline in serum and saliva after administration of 3 mg/kg of theophylline to smoker Subject J. S. *during* and 3 mo *after* cessation of cigarette smoking. The solid lines were computer-fitted to the data.

"Zipax" SCX column. The mobile phase was 0.66% acetic acid, the pressure was 1,200 psi, and the detector was set at 280 nm. After β-hydroxypropyltheophylline was added as an internal standard, the serum or saliva samples were extracted into 10 ml of chloroform containing 5% isopropyl alcohol. The organic solvent was evaporated and 0.1 ml of 0.66% acetic acid was used to reconstitute the residue for injection onto the column. This particular analytical procedure is specific for theophylline and is not affected by at least four of its major metabolites, caffeine, and theobromine.[10] Thiocyanate concentrations in serum were measured by the colorimetric method of Pettigrew and Fell.[20]

Using nonlinear least-square regression analysis,[15] the data were fitted to appropriate pharmacokinetic equations for a one-compartment model. Parameters that were calculated include the half-life, apparent volume of distribution, and body clearances[14] of theophylline.

Results

Serum and saliva theophylline concentrations from one of the heaviest smokers are plotted as a function of time in Fig. 1. The descending portions of the serum and saliva curves were used to generate a least-square half-life and the

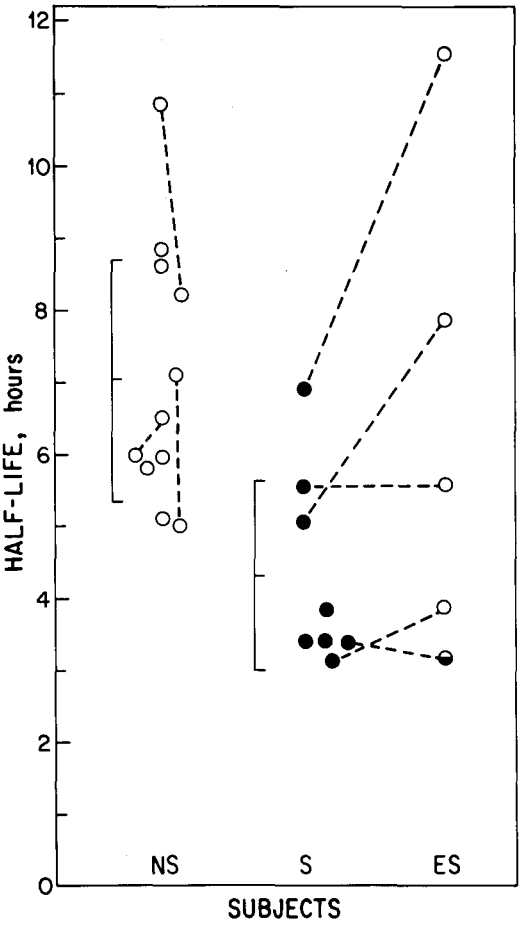

Fig. 2. Elimination half-life of theophylline in nonsmokers *(NS)* and cigarette smokers *(S)*. Some of the smoking subjects were studied after stopping smoking for 3 mo *(ES)*, but one of the latter did not fully quit smoking (◒). Broken lines connect data from repeated studies in individual subjects. The vertical lines depict the mean ± 1 standard deviation of the data sets.

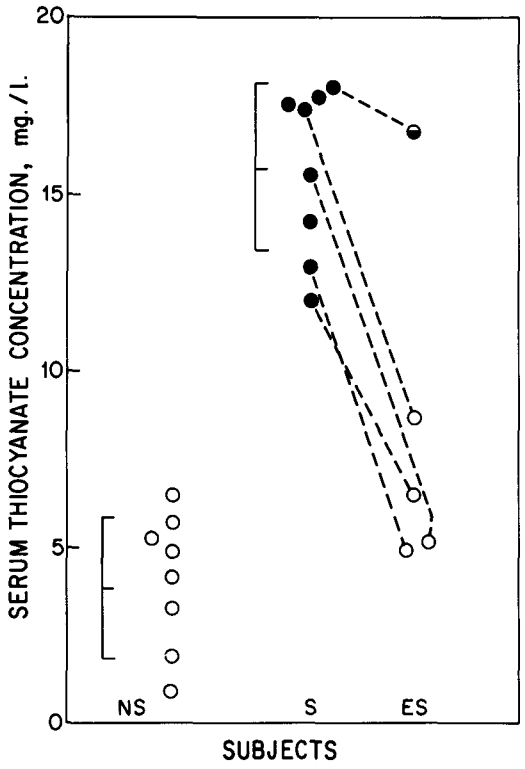

Fig. 3. Serum thiocyanate concentrations in the three groups of subjects. Symbols are defined as in Fig. 2.

area under the serum concentration vs time curve was obtained by trapezoidal integration to allow calculation of the apparent volume of distribution and body clearance. The data in Fig. 1 show little difference while the subject was smoking and after she had discontinued smoking for three months.

A summary of the half-lives of theophylline in the three groups of subjects (nonsmokers, smokers, and ex-smokers) is shown in Fig. 2. The mean half-life in smokers was 4.31 (SD = 1.35) hr, which is ($p < 0.005$) shorter than the mean value of 7.03 (SD = 1.69) hr in the nonsmokers. Following cessation of smoking, 3 subjects had a longer half-life and 2 subjects exhibited no change. It is believed that one of the latter subjects did not entirely discontinue smoking as he professed. Evidence for this can be noted from the serum concentrations of thiocyanate that are plotted in Fig. 3. Much higher levels of serum thiocyanate, a biotransformation product of cyanide that is inhaled during smoking (and ingested from other sources), was found in smokers (15.7 ± 2.4 mg/L) than in nonsmokers (3.8 ± 2.0 mg/ L). Smokers who stopped smoking had a pronounced fall in serum thiocyanate concentrations whereas the one smoker who probably did not stop entirely had only a small change in thiocyanate concentration. The range of thiocyanate concentrations in the two groups of subjects agree well with

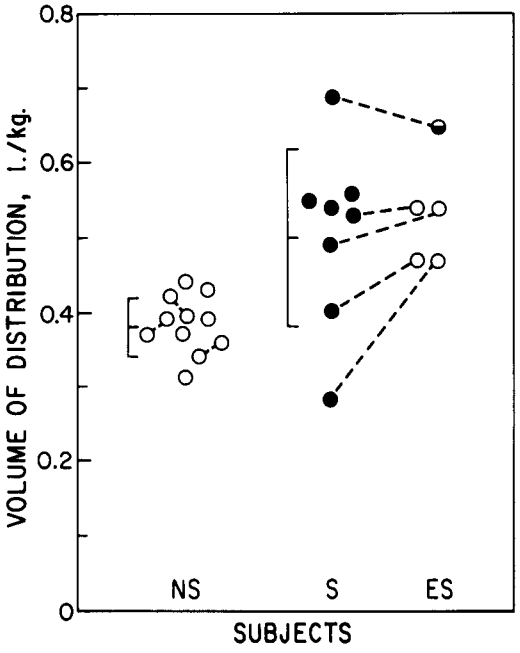

Fig. 4. Apparent volume of distribution of theophylline in the three groups of subjects. Symbols are defined as in Fig. 2.

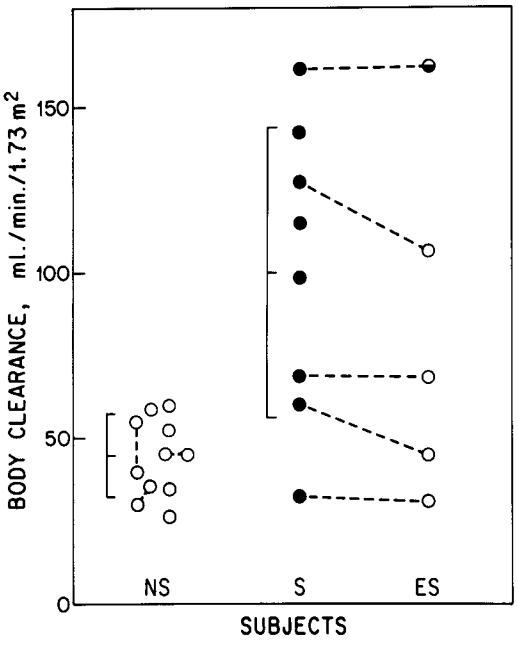

Fig. 5. Body clearances of theophylline in the three groups of subjects. Symbols are defined as in Fig. 2.

values cited elsewhere for smokers and nonsmokers.[20]

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 (Fig. 4). This difference is significant ($p < 0.025$). The alterations in distribution volume that occurred on cessation of smoking were not significant.

The parameter that best reflects the total elimination rate of a drug is the body clearance. Theophylline is largely metabolized with about 10% of a dose excreted unchanged in urine. Thus the body clearance of the bronchodilator primarily reflects its rate of biotransformation. As shown in Fig. 5, the nonsmokers had a very narrow range of body clearance values, averaging 44.5 ± 12.6 ml/min/1.73 m^2. The smokers, on the other hand, exhibited body clearances that were larger ($p < 0.005$) and more variable, averaging 100.4 ± 44.0 ml/min/1.73 m^2. The clearances that were found after smoking was discontinued in 4 subjects were not significantly modified.

Three of the nonsmokers had been heavy cigarette smokers who had stopped smoking 2, 5, and 6 yr prior to their participation in this study. Data from these subjects were indistinguishable from the other nonsmokers. Thus it appears that between 3 mo and 2 yr may be necessary for normalization of the effect of smoking on theophylline pharmacokinetics. This long period may be related to the fact that benzpyrene and the polycyclic hydrocarbons, the probable enzyme inducers in cigarette smoke,[19] which are highly lipid-soluble materials, may be eliminated very slowly from the body.

The relationship between body clearances of theophylline and serum concentrations of thiocyanate was also examined. There was a good correlation between these two parameters in the nonsmokers and smokers ($r = 0.785$, $p < 0.001$). Additional inspection of the data included performing a multiple linear regression analysis between body clearances of theophylline, serum thiocyanate concentrations, and daily caffeine ingestion (number of cups of tea

and coffee consumed). Caffeine intake yielded only a slight improvement in the correlation with theophylline body clearances (multiple correlation coefficient = 0.797) and was thus not a significant factor affecting our data.

Discussion

Cigarette smoke contains, among other materials, carbon monoxide, hydrogen cyanide, acrolein, nitric oxide, alkaloids, tars, polycyclic hydrocarbons, polyphenols, pigments, and metals.[12] Thus it is not surprising that cigarette smoking is capable of modifying the kinetics of some drugs. Data in earlier studies with pentazocine,[11] phenacetin,[19] and nicotine[1] are consistent with the induction of microsomal drug-metabolizing enzymes resulting in more rapid biotransformation of these compounds. Since theophylline is largely metabolized in the liver by oxidative mechanisms[5] that are subject to enzyme induction by phenobarbital,[21] it is probable that the same phenomenon accounts for the differences in elimination of theophylline between the smokers and nonsmokers.

Caffeine ingestion was somewhat greater in the smokers and was therefore examined as a variable contributing to the larger body clearances in the smokers. Since caffeine is capable of inducing drug-metabolizing enzymes in animals,[18] a similar effect might be possible in man. However, adding caffeine ingestion to a linear regression analysis as a second factor determining body clearances of theophylline did not improve the correlation of the data. Thus at least one secondary difference between the two groups of subjects can be ruled out as a quantitatively significant additional variable.

The larger apparent volume of distribution of theophylline in smokers is difficult to rationalize. A well-known effect of cigarette smoking is peripheral vasoconstriciton. This factor may alter the distribution of theophylline by inhibiting the return of theophylline from body tissues. Dales and co-workers[6] have noted that cigarette smokers tend to have slighter physiques with less subcutaneous fat than nonsmokers. It is not certain, however, whether theophylline distribution may relate best to lean or total body weight. Correction of the volumes of distribution for the estimated lean body weight (lbw) yields slightly closer values for the smokers (0.492 L/kg lbw) and nonsmokers (0.403 L/kg lbw). The other complicating factor in examining the volumes of distribution is that the theophylline was administered orally and any effect of smoking on the bioavailability of theophylline may modify the volume estimates.

Overall, the data in our study are similar in range to that of parameter values reported in other studies in relatively young, healthy adults. Jenne and associates[9] found half-lives ranging from 3.0 to 9.5 hr, an apparent volume of distribution of about 0.5 L/kg., and body clearances ranging from 47 to 133 (mean, 82 ml/min). Mitenko and Ogilvie[16] report body clearances that range from 47 to 140 ml/min (mean, 84 ml/min). Ellis, Koysooko, and Levy[7] found a half-life range of 3.5 to 8.0 (mean, 5.8 hr), apparent volumes of distribution between 0.34 and 0.59 (mean, 0.45) L/kg, and body clearances of 46 to 107 (mean, 66) ml/min after intravenous administration of theophylline. These three studies probably contained a mixture of smoker and nonsmoker subjects, which partly accounts for their appreciable variability.

As our study was completed, Jenne and co-workers[8] reported half-lives of theophylline in a group of young subjects in relation to their smoking habit. Their 10 cigarette smokers had an average half-life of 4.1 ± 1.2 hr, while 14 nonsmokers had an average half-life of 7.2 ± 1.8 hr. a significant difference. These are similar to our findings (Fig. 2) and further confirm that cigarette smoking is a major determinant of the variability in theophylline disposition in young adults. Pharmacokinetic studies with theophylline should therefore include a record of smoking and use of other enzyme inducers.

Our data indicate that young patients who smoke and who require theophylline will probably need daily dosages about twice those needed by nonsmokers. Since cigarette smoking causes greater variability in theophylline clearances and has a direct irritant effect on the lungs which is usually accompanied by increasing mucus production, it is likely that the response to theophylline therapy in smokers will be more

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