Lack of Effect of Withdrawal from Cigarette Smoking on Theophylline Pharmacokinetics

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The intravenous disposition of theophylline was determined in 12 healthy young male smokers during periods of smoking and short-term withdrawal (24 to 36 hours), using a crossover design. Median half-life, clearance, volume of distribution, hepatic extraction, and intrinsic clearance of theophylline during withdrawal were within ±5% of the corresponding median control (smoking) parameters and were normal in comparison with values published for smokers. The lack of change in the pharmacokinetic profile of theophylline indicates that adjustment of the dosage regimen should not be necessary immediately after smoking withdrawal.

Theophylline is widely recognized as a valuable drug for the treatment of bronchospasm in pulmonary disease. Increased theophylline biotransformation secondary to the induction of hepatic metabolic enzymes by cigarette smoking has been documented thoroughly.[1-3] Accordingly, active smokers may require doses 1½ to two times those needed for nonsmokers to maintain comparable steady-state plasma concentrations.

The disposition of theophylline in smokers who quit and exsmokers has not been studied to the same extent. Several studies have shown no change or moderate changes in theophylline body clearance in smokers who stopped for three months to ten years.[1-3] Nevertheless, the *FDA Drug Bulletin* has published warnings of impending toxicity in cases in which dosage regimens are not adjusted for patients who have withdrawn from smoking.[4] No specific time frame for the adjustment was discussed.

Information is lacking on the disposition of theophylline and other drugs during the period immediately after withdrawal from smoking. The effects of complex cardiovascular reactions and emotional stresses on drug disposition during the first days after smoking cessation have not been studied.[5-7] Theophylline disposition during this phase of withdrawal merits attention since patients with pulmonary disease are often urged to quit smoking or are required to stop during periods of hospitalization.

In this report, a two-period crossover study was used to compare theophylline pharmacokinetics between periods of smoking and short-term smoking withdrawal. This work is part of a larger study of the effects of short-term tobacco withdrawal on the pharmacokinetics of several drugs.[8]

METHODS

Subjects

Twelve healthy male subjects, all of whom were long-term cigarette smokers, participated in the study. The subjects' median age, median body weight, and median daily cigarette consumption were 23.5 years, 76.6 kg, and 25 per day, respectively. Each volunteer signed an informed consent agreement before admittance to the study, after which each was given a complete physical examination including comprehensive blood analysis. Subjects were instructed to avoid xanthine-containing foods for 48 hours before arrival for the study. The diet during all phases of the study was free of xanthine-containing foods.

Study Design

Subjects were randomly assigned to one of two treatment groups, the first of which was withdrawn from smoking during the first period of the trial. The second treatment group was allowed to smoke according to habit during the first period. Both groups were crossed over to the opposite treatment during the second period, which was scheduled after a one-week washout. Subjects who stopped smoking

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did not smoke for 24 hours before the administration of drugs on each trial day and continued to abstain until all sampling was completed. Indocyanine green and antipyrine were administered intravenously (IV) prior to theophylline dosing for the purpose of determining their respective clearances under the trial conditions, the results of which will be reported elsewhere.[8]

Theophylline was administered as aminophylline via a short-term infusion into a forearm vein at the rate of 48 mg/min. Blood samples were drawn by means of venipuncture of the forearm veins of the contralateral arm at 10, 20, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after cessation of the infusion. Not all subjects tolerated the infusion well; some experienced pain in the upper arm. Accordingly, some infusions were stopped before completion, resulting in the administration of different doses to different subjects. The actual doses administered are listed in Table I.

Analytic Methods

Plasma harvested from heparinized whole blood samples was analyzed for theophylline content, using a sensitive and reproducible high-performance liquid chromatography (HPLC) micromethod developed in our laboratories. An aliquot of 0.1 mL of plasma was vortexed for 30 seconds with 1 mL of an equal mixture of chloroform and isopropyl alcohol (isopropanol) that contained 3 μg of the internal standard 8-chlorotheophylline (8-CT). The biophasic mixture was centrifuged for five minutes, and the lower organic phase was removed by means of aspiration and evaporated at 60°C under nitrogen gas flow. The residual material was reconstituted in 50 μL of methanol, 20 μL of which was injected onto the C-18 reverse-phase column (μBondapak C-18, Waters Associates, Milford, MA). The samples were eluted with a mobile phase containing 10% acetonitrile in 0.1 M pH 4 sodium acetate buffer at a flow rate of 2 mL/min. Detection was by ultraviolet (UV) absorbance at 254 nm, and the absolute retention times of theophylline and 8-CT were 4.6 and 9.1 minutes, respectively. The method was calibrated from 0.5 to 15.0 μg/mL plasma by the method of peak height ratios obtained from standards made by spiking blank human plasma. The coefficient of variation for replicate samples at 0.5 μg/mL was 9.3%; for samples in the range of 1-15 μg/mL, it was less than 5%. No interfering peaks, including those from potential theophylline metabolites, were encountered in any sample.

TABLE I

Theophylline Doses Administered (Treatment)

Subject	Period 1 Dose*	Period 2 Dose*
019	231.6(w)	154.4(s)
089	231.6(s)	202.7(w)
139	386.0(s)	386.0(w)
145	386.0(s)	386.0(w)
151	270.2(s)	308.8(w)
164	231.6(w)	231.6(s)
203	289.5(w)	231.6(s)
204	386.0(w)	386.0(s)
253	386.0(w)	386.0(s)
262	386.0(s)	386.0(w)
263	386.0(w)	386.0(s)
268	231.6(s)	231.6(w)

*Theophylline dose in milligrams, administered as aminophylline. Intended dose = 386 mg theophylline.
s = smoking; w = withdrawal.*

Pharmacokinetic Analysis

Theophylline concentration-time data were fitted with a monoexponential pharmacokinetic model describing disposition after cessation of an IV infusion that did not reach steady state. The equation

$$C = R_o/CL_p \times (1 - e^{(-\lambda_z \times T)}) \times e^{(-\lambda_z \times t_{pi})}$$

in which R_o is the infusion rate, T is the duration of the infusion, t_{pi} is the time postinfusion, CL_p is the plasma clearance rate, and λ_z is the first-order elimination rate constant, was fitted to each data set, using the computer program NONLIN.[9] Values for the volume of distribution (V_z) and the elimination half-life ($t_{1/2}$) were calculated by the program, using established methods.[10]

Parameters for the hepatic clearance model as described by Wilkinson and Shand[11] were calculated from the above parameters and from hepatic blood flow (Q_h) estimated from the indocyanine green clearance measured in each subject immediately before theophylline administration.[8] Theophylline CL_p value were converted to blood clearances (CL_b) by dividing each CL_p by the blood-to-plasma distribution ratio.[12] The distribution ratio of 0.82, as determined by Mitenko and Ogilvie,[13] was used for this conversion. The hepatic extraction ratio (E) and the intrinsic clearance (CL_{int}) were calculated[11] as follows:

$$E = CL_b/Q_h$$

$$CL_{int} = Q_h \times E/(1 - E)$$

Statistical Analysis

Pharmacokinetic parameters resulting from, or dependent on, nonlinear curve fitting were evaluated statistically, using nonparametric procedures. These methods were selected for their robustness against bias introduced in the curve-fitting process[14,15] and because the assumptions nec-

essary for their application to data from pharmacokinetic trials can be realistically met.[16,17] The nonparametric descriptive statistics median (Med) and the semi-interquartile range (SIQR) and a coefficient of variation (COV) equal to the SIQR divided by the median were substituted for their parametric counterparts of mean, standard deviation, and coefficient of variation, respectively.[18] Treatment, period, and residual effects associated with the two-period crossover model were evaluated using methods described by Koch.[19] An estimator of smoking-withdrawal differences (δ) and its 95% confidence interval were calculated for each parameter.[20] The δ values and their confidence intervals were expressed as a percentage of control smoking medians, represented by δ%.

RESULTS

Theophylline pharmacokinetic and hepatic clearance model parameters from smoking (control) and withdrawn conditions are listed by subject in Table II. Mean plasma concentration-time data for both conditions are shown in the Figure. No significant differences between treatments

TABLE II

Pharmacokinetic and Hepatic Clearance Model Parameters for Theophylline

Subject	$t_{½}$ (hr)	CL_b (mL/min/kg)	V_z (L/kg)	E	CL_{int} (mL/min/kg)
		Smoking			
019	5.6	1.24	0.49	0.10	1.37
089	6.2	1.00	0.44	0.07	1.08
139	5.7	1.15	0.46	0.08	1.25
145	3.4	1.89	0.46	0.12	2.16
151	5.6	1.14	0.45	0.08	1.24
164	4.6	1.64	0.54	0.11	1.83
203	4.0	1.94	0.55	0.10	2.15
204	4.4	1.43	0.45	0.08	1.56
253	5.1	1.51	0.55	0.07	1.63
262	5.7	1.25	0.51	0.10	1.39
263	2.8	2.73	0.54	0.10	3.03
268	5.0	1.16	0.42	0.08	1.26
Med	5.1	1.34	0.48	0.09	1.48
SIQR	0.82	0.37	0.05	0.01	0.45
COV	0.16	0.28	0.09	0.10	0.31
		Withdrawn			
019	5.6	1.21	0.48	0.06	1.29
089	6.6	0.97	0.46	0.05	1.03
139	6.0	1.20	0.51	0.07	1.30
145	3.7	1.89	0.50	0.11	2.12
151	5.4	1.23	0.47	0.09	1.34
164	4.8	1.60	0.55	0.09	1.75
203	4.4	1.72	0.54	0.10	1.90
204	4.2	1.49	0.44	0.09	1.64
253	5.0	1.69	0.59	0.10	1.87
262	6.5	1.17	0.54	0.10	1.31
263	2.9	2.51	0.52	0.12	2.87
268	4.5	1.45	0.46	0.09	1.59
Med	4.9	1.47	0.51	0.09	1.62
SIQR	0.92	0.26	0.04	0.02	0.30
COV	0.18	0.18	0.08	0.17	0.19

$t_{½}$ = elimination half-life; CL_b = total blood clearance; V_z = volume of distribution; E = hepatic extraction ratio; CL_{int} = intrinsic clearance; Med = median; SIQR = semi-interquartile range; COV = coefficient of variation.

were found for theophylline $t_{1/2}$, CL_b, V_z, E, or CL_{int}, as summarized in Table III. Residual and period effects associated with the two-period crossover design were absent. Estimates for $\delta\%$ show that during withdrawal, all parameters were within 5% of smoking control values, indicating that clinically significant changes in theophylline disposition did not occur during short-term withdrawal.

DISCUSSION

Clinically or statistically significant changes in any theophylline pharmacokinetic parameter were not observed during acute smoking withdrawal. The median values for theophylline $t_{1/2}$, V_z, and CL_b given in Table II agree closely with those found in smokers by other researchers.[1,3,21-24] Our values for the hepatic extraction of ratio of 0.09 are comparable to the estimate of 0.1 made by Ogilvie.[2] Since theophylline has low extrahepatic elimination and Q_h remained constant throughout the study, estimates of CL_{int} paralleled those of CL_b in each subject.[25]

The use of nonparametric methods for descriptive and decisive purposes in this study is well founded. When a set of parameters is relatively small and subject to the presence of outliers, as with the data from this and many other pharmacokinetic studies, the nonparametric estimators used here will in general be more efficient.[18] Steinijans and co-workers[16] demonstrated that the pharmacokinetic parameters of theophylline related to the elimination-rate constant are log-normally distributed when the drug is given by short-term infusion. More recently, Steinijans and Diletti[17] showed that the use of nonparametric methods in theophylline bioavailability testing is as efficient as standard methods but is independent of several restrictive assumptions associated with parametric procedures. The nonparametric analysis of two-period crossover trials used in our study was discussed by Koch[19] and was extended to include point and interval estimators by Cornell.[26] The application of these methods may be more appropriate when the sample size is small and the true distribution underlying the sample set is not known or not readily determined.

The results of this trial reinforce our findings of no effect of smoking withdrawal on the pharmacokinetics of other drugs.[8] Withdrawal-related differences in antipyrine distribution were not observed in the same subjects under identical trial conditions. The similarity in behavior of theophylline and antipyrine in this trial may be indicative of a trend, since both compounds are extensively biotrans-

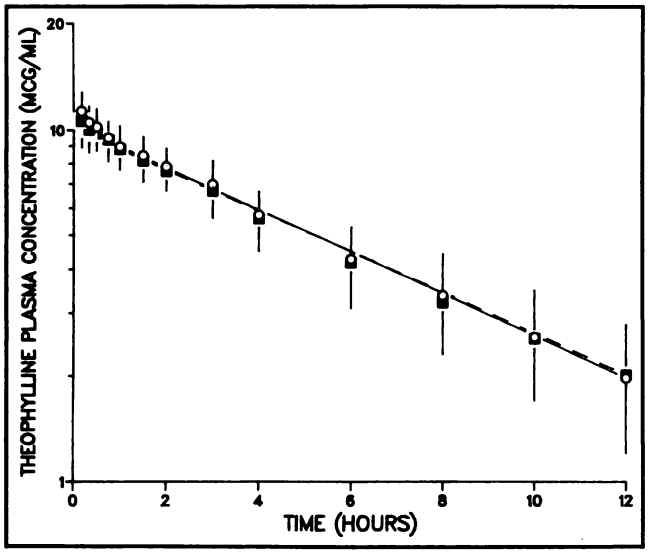

Figure. Mean (± SD) theophylline plasma levels for smoking (O) and withdrawn (■) conditions. The solid and dashed lines are linear regression fit lines from the smoking and withdrawn data, respectively.

TABLE III

Results of Hypothesis Testing, δ (95% CI), and δ%* (95% CI)

Parameter	Main Effects			Median Control	δ	95% CI		δ%*	95% CI	
	Residual	Treatment	Period			LL	UL		LL	UL
$t_{1/2}$ (hr)	NSD	NSD	NSD	5.09	0.235	−0.18	0.45	104.62	96.46	108.85
CL_b (mL/min/kg)	NSD	NSD	NSD	1.34	0.005	−0.092	0.098	100.37	91.62	108.92
V_z (L/kg)	NSD	NSD	NSD	0.48	0.014	0.00	0.031	102.94	100.0	106.39
E	NSD	NSD	NSD	0.09	0.0	−0.015	0.010	100.00	83.33	111.11
CL_{int} (mL/min/kg)	NSD	NSD	NSD	1.48	−0.015	−0.10	0.125	98.98	93.22	108.47

**δ% = (control + δ)/control × 100%.*
LL = lower limit of 95% CI; UL = upper limit of 95% CI; NSD = no significant differences; $t_{1/2}$ = elimination half-life; CL_b = total blood clearance; V_z = volume of distribution; E = hepatic extraction ratio; CL_{int} = intrinsic clearance; CI = confidence interval.

formed and have low hepatic extraction. Previous work has demonstrated that enzyme induction affecting these drugs is relatively slow to reverse.[1,3,27] However, possible changes in distribution as a function of withdrawal-induced cardiovascular stress[28] or of the effect of nicotine peripheral vasoconstriction could not be ruled out.[1] These changes were either absent or of negligible magnitude during the withdrawal periods in our studies.

The importance of maintaining theophylline plasma levels within a well-defined range has been established thoroughly. One of our research goals was to formulate an approach for correcting dosage regimens during smoking withdrawal if necessary. Data from this study and from the work of others now cover the entire time frame from the time of cessation to several years after smoking withdrawal, making it possible to address this question. Hunt and associates[1] observed no change in theophylline clearance after three months of withdrawal, while Powell and colleagues[3] reported a 20% decrease in clearance in subjects who stopped smoking for two to ten years. No rapid or large changes in theophylline clearance have been reported at any time after smoking withdrawal. The previously recommended dose reduction appears unnecessary on a pharmacokinetic basis.[4]

Contemporary monitoring required for safe and effective theophylline use should be sufficient to detect any postwithdrawal changes in clearance that may occur.

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