Time response of cytochrome P450 1A2 activity on cessation of heavy smoking

Background and Objective: **Cytochrome P450 (CYP) 1A2 activity is induced by cigarette smoking. Thus smoking cessation in patients while they are undergoing therapy with a CYP1A2 substrate such as theophylline or clozapine increases its concentrations and may cause adverse effects. Our objective was to determine the time course of CYP1A2 activity changes after smoking cessation in heavy smokers as the basis for dosing adaptation schemes.**

Methods: **The study was conducted in 8 men and 4 women (all white) who smoked 20 cigarettes or more per day. Sudden smoking cessation was carried out after a 14-day run-in period. Subjects were phenotyped for CYP1A2 activity at 6, 4, and 1 day before smoking cessation and at 0, 1, 2, 3, 6, 8, 10, and 13 days thereafter by use of the paraxanthine-to-caffeine ratio in plasma 6 hours after a 148-mg caffeine test dose. A monoexponential decay of CYP1A2 activity to a residual value was fitted to the data by nonlinear regression analysis.**

Results: **On cessation of smoking, initial caffeine clearance (estimated geometric means and 95% confidence intervals) decreased significantly ($P < .01$), by 36.1% (30.9%-42.2%), from 2.47 mL · min^{-1} · kg^{-1} body weight (2.03-3.00 mL · min^{-1} · kg^{-1} body weight) to a new steady state of 1.53 mL · min^{-1} · kg^{-1} body weight (1.24-1.89 mL · min^{-1} · kg^{-1} body weight). The apparent half-life of CYP1A2 activity decrease was 38.6 hours (27.4-54.4 hours).**

Conclusion: **Doses of CYP1A2 substrates with a narrow therapeutic range should be decreased immediately on cessation of heavy smoking. As a rule of thumb, a stepwise daily dose reduction of approximately 10% until the fourth day after smoking cessation is proposed, which should be accompanied by therapeutic drug monitoring. (Clin Pharmacol Ther 2004;76:178-84.)**

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The cytochrome P450 (CYP) enzyme 1A2 is involved in the metabolism of many drugs, such as theophylline,[1] clozapine,[2] tacrine,[3] propranolol,[4] melatonin,[5] verapamil,[6] and so on. Plasma concentrations of such drugs, therefore, depend on the activity of this enzyme. Large interindividual and intraindividual variability of CYP1A2 activity has been found in humans.[7] Because some of the substances metabolized by CYP1A2 have a narrow therapeutic range (eg, theophylline and clozapine), actual individual enzyme activity may have an important effect on their efficacy and tolerability, and a correspondingly individualized dose is often required for such drugs.

The pronounced variability in CYP1A2 activity is partly due to the fact that it is induced or inhibited by other drugs, by environmental compounds, and by dietary or lifestyle-related factors. Cigarette smoking has a well-known effect that has been quantified in a larger study, in which a 1.72-fold higher enzyme activity in heavy smokers compared with nonsmokers was found.[8]

Sudden abolition of CYP1A2 induction caused by smoking cessation has the potential to precipitate adverse drug reactions. Case reports describing adverse reactions caused by elevated concentrations of clozapine or olanzapine after smoking cessation suggest that dose adjustment should be conducted whenever patients cease smoking under treatment with CYP1A2-metabolized drugs.[9-13]

This study was carried out to examine the time response of CYP1A2 activity on cessation of heavy smoking so that appropriate dosing adaptation schemes for CYP1A2 substrates could be developed.

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METHODS

The study was conducted after approval of the study protocol by the independent Ethics Committee of the Medical Faculty of the University of Cologne, Köln, Germany. All volunteers gave written informed consent.

Subjects. Twelve volunteers who smoked 20 cigarettes or more per day were included in the study. They were healthy as assessed on the basis of medical history, clinical examination, electrocardiography, and routine laboratory screening. Additional information documented included body height, body weight, age, usual average daily methylxanthine consumption, smoking behavior within the last 12 months, and exposure to xenobiotics (eg, occupational). Subjects receiving any medication including oral contraceptives within 4 weeks before the investigation were excluded from the study.

Study procedure. The study was conducted in an ambulatory setting. Subjects maintained a diet to minimize factors that could possibly change CYP1A2 activity during the study. They abstained from alcohol, broccoli, cauliflower, grapefruit products, grilled meat, drugs, and methylxanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, and so on) other than the caffeine provided as a test substance. The clinical part of the investigation consisted of the run-in phase and the actual smoking cessation period, each lasting 14 days. The run-in phase was conducted to achieve a new steady state of CYP1A2 activity after the dietary changes, to gather information regarding actual smoking behavior via a subject's diary, and to provide a starting point for CYP1A2 activity before the intervention of smoking cessation. Subjects reported to the study site on days −6, −4, and −1 relative to intervention for CYP1A2 phenotyping. To this end, a blood sample of 7.5 mL was taken, and the subjects received a caffeine test dose, were weighed, and returned 6 hours later for a second blood sampling. Caffeine is eliminated almost exclusively by CYP1A2-mediated metabolism and is fully validated as a CYP1A2 phenotyping drug.[14] It was administered as 1 cup of coffee every morning, made from 5 g of regular instant coffee (Nescafé Gold; Nestlé, Frankfurt am Main, Germany) with a caffeine content of 148 mg (as provided by the manufacturer and confirmed by HPLC analysis). Intake of coffee was done under supervision on those days when subjects reported to the study site for phenotyping. For the remaining days, study participants were provided with prepacked coffee powder to be brewed with hot water and taken at home. The time of intake was documented by study personnel and by the participants, respectively. After sudden smoking cessation, phenotyping was carried out on days 0, 1, 2, 3, 6, 8, 10, and 13. For compliance control with regard to nicotine abstinence, cotinine in urine was estimated by a semiquantitative test (Accutest NicAlert; Jant Pharmacal Corporation, Encino, Calif) on 9 of 11 phenotyping days.

Analytic assay. Caffeine and paraxanthine concentrations in plasma samples were estimated by an HPLC method partly based on published methods.[14] In brief, a 750-μL plasma aliquot was prepared by addition of 50 μL internal standard (200 mg/L hydroxyethyltheophylline) and 250 μL ammonium acetate solution (2 g ammonium acetate per milliliter of water). The methylxanthines were extracted by adding 5 mL dichloromethane and mixing for 10 minutes in a tumble mixer. The organic phase was then transferred to another glass tube and evaporated in a speed vacuum (RC 10-22; Jouan GmbH, Unterhaching, Germany). The solid residuum was solubilized in 150 μL mobile phase.

Twenty microliters of this solution was injected onto a Nucleosil 100 C18 reversed-phase column (column dimensions, 125 mm · 4 mm; 5 μm particle size; Macherey-Nagel, Düren, Germany) and eluted by use of a 4-mmol/L acetic buffer (pH 4.0) containing 1% acetonitrile, 1% methanol, and 1.6% tetrahydrofurane (wt/wt). The initial flow was increased from 0.8 mL/min to 1.8 mL/min within 13 minutes. Calibration was based on peak height ratios for ultraviolet absorption at 278 nm and data point weighting by the inverse of concentrations. Calibration and quality-control samples were prepared from plasma of a subject with at least 3 days of methylxanthine abstinence, which was checked for absence of caffeine and paraxanthine.

Sample stability was confirmed with respect to freeze-thaw cycles, processing time, and autosampler residence time. Within- and between-day precision (coefficient of variation for repeated measurements) and accuracy (mean difference between estimated and true concentration) were better than 10% in the concentration range of the quality control samples (200 nmol/L to 40,000 nmol/L for caffeine and paraxanthine), which also defined the lower and upper limits of quantification, respectively. Recovery was better than 90%.

Treatment of data. Calculations were made by use of Microsoft Excel 2000 (Microsoft Corporation, Redmond, Wash). Calculations and tests not available with this software were carried out by use of SPSS 11.0 (SPSS Inc, Chicago, Ill).

Caffeine clearance was calculated by use of the paraxanthine-to-caffeine concentration ratio (see Equa-

tion 1) in plasma approximately 6 hours after the caffeine test dose as reported in a previous study.[8] A second estimate of caffeine clearance based on caffeine concentrations only was used in addition only as a compliance control regarding additional dietary caffeine intake as described.[8] The paraxanthine-to-caffeine ratio 6 hours after dosing and the derived estimate of caffeine clearance have previously been validated as reliable metrics for CYP1A2 activity.[14]

$$Cl = \frac{C_{PX,postdose} \cdot 11.681}{C_{CAF,postdose} \cdot \Delta t_{postdose\text{-}predose}}$$

in which Cl is the estimated caffeine clearance, $C_{PX,postdose}$ is the molar concentration of paraxanthine in the postdose sample, $C_{CAF,postdose}$ is the molar concentration of caffeine in the postdose sample, and $\Delta t_{postdose\text{-}predose}$ is the exact time difference between the administration of the caffeine test dose and the time of the postdose plasma sample.

Because of inadvertent intake of caffeine by 1 subject at the first phenotyping day, caffeine clearance data for this subject and day have been excluded from the analysis.

A monoexponential decay of CYP1A2 activity to a residual value was fitted to the data of every individual subject by nonlinear regression analysis according to equation 2. The model was estimated by use of the least squares method.

$$Cl_t = (Cl_{start} - Cl_{end}) \cdot e^{-k_{CYP1A2} \cdot t} + Cl_{end}$$

in which t is time relative to smoking cessation, Cl_t is caffeine clearance at time t, Cl_{start} is caffeine clearance before intervention, Cl_{end} is caffeine clearance when a new steady state was reached after intervention, and k_{CYP1A2} is the CYP1A2 activity change rate constant.

Cl_{start} was defined as the geometric mean of the 3 caffeine clearance values of the run-in phase, and whenever clearance values are given relative to the starting point, this value is defined as 100%. Logarithmic transformation of data was applied for statistical tests. To test the general hypothesis of whether there were indeed significant changes in caffeine clearance after smoking cessation, the SPSS general linear model for repeated measurements was applied for the entire data set. For descriptive evaluation of distinctions between each time point with CYP1A2 phenotyping and the individual starting point, 2-sided *t* tests for paired samples were used. Geometric mean time courses of observed and estimated caffeine clearance values were presented, together with the respective 95% confidence interval for observed values based on log data. Pearson correlation was calculated between the relative decrease in caffeine clearance after intervention and the number of cigarettes smoked during the last 1 to 5 days before intervention.

RESULTS

Four female and 8 male white subjects participated in the study. The mean age (±SD) was 29.9 ± 4.9 years, the mean body weight at the inclusion examination reached 74.7 ± 13.7 kg, and the mean body mass index was 22.7 ± 2.4 kg · m^{-2}. The mean number of cigarettes smoked per day in the 2 weeks before intervention (smoking cessation) ranged from 22.3 ± 6.0 (day −4) to 27.7 ± 11.3 (day −9).

In 3 subjects, urinary cotinine levels marginally exceeded the abstinence threshold during the smoking cessation period on 1 occasion each. Before the test was conducted, 2 of these subjects had reported passive smoking on their documentation sheet (subject's diary) as a result of occupational reasons and a party, respectively. The third subject reported passive smoking because of living conditions at home after being confronted with the result of the test.

After the intervention of smoking cessation, a statistically significant ($P < .01$) decrease in individual caffeine clearance depending on CYP1A2 activity was observed. Individual time courses of caffeine clearance are presented in Fig 1. Starting on day 6 after smoking cessation, the decrease was present in all subjects. Geometric means of measured caffeine clearance relative to the starting point before intervention and the respective 95% confidence intervals are shown in Fig 2. This figure also includes the time course of means of caffeine clearance data according to the fitted model.

In Table I individual and summary data resulting from the calculation of this model by nonlinear regression analysis are presented.

As a basis for dose adjustments, geometric means and ranges for the relative reduction in CYP1A2 activity were 12.3% (3.4%-20.6%), 20.1% (6.4%-32.6%), 25.0% (9.1%-41.3%), 28.2% (11.4%-47.0%), and 36.1% (24.4%-58.4%) estimated at 1, 2, 3, and 4 days after smoking cessation and finally at steady state, respectively.

Pearson correlation showed no significant relationship ($P > .05$) between the individual estimated relative decrease in caffeine clearance after intervention and the mean number of cigarettes smoked during days −5 to −1 before the intervention.

DISCUSSION

The study was conducted to determine the time course of CYP1A2 activity after cessation of heavy smoking. A rapid exponential decrease was observed

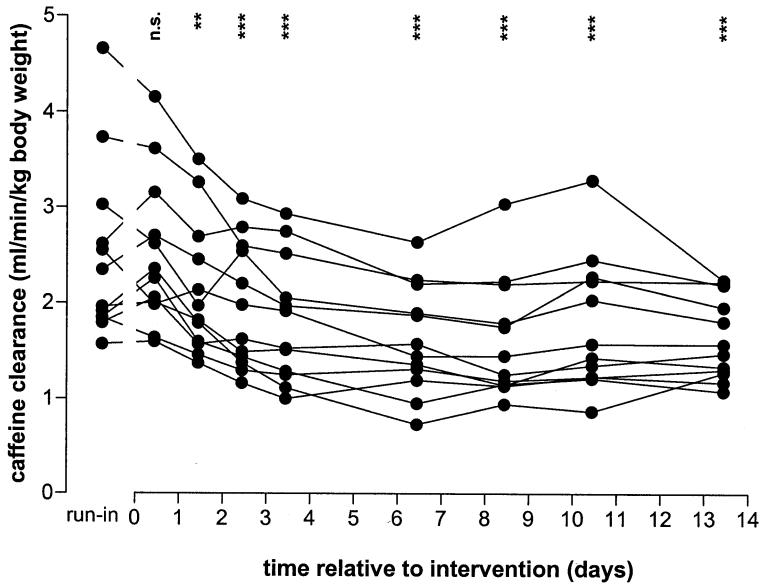

Fig 1. Individual time courses of caffeine clearance estimated from paraxanthine/caffeine plasma ratios after the intervention of smoking cessation. The "run-in" value is the individual geometric mean of values on days −6, −4, and −1. ns, Not significant ($P \geq .05$); *2 asterisks*, $P < .005$; *3 asterisks*, $P < .0005$; these are for descriptive comparisons relative to individual starting points by use of 2-sided *t* tests for paired samples.

until a new steady state was reached after approximately 1 week.

Given the ambulatory setting of the study, compliance problems cannot be ruled out completely. Therefore we implemented 4 different strategies to address this problem, including supervision of caffeine intake on phenotyping days, conduction of cotinine urine tests, the use of a control calculation for caffeine clearance (see Methods section), and a sanction-free handling of noncompliance reported by the volunteers. These measures are considered as appropriate both to avoid and to recognize major deviations from the study protocol.

Our results confirm the well-known inducing effect of cigarette smoking on CYP1A2.[15-17] Geometric mean caffeine clearance decreased 1.61-fold after smoking cessation, from 2.47 mL $\cdot$ min^{-1} $\cdot$ kg^{-1} to 1.53 mL $\cdot$ min^{-1} $\cdot$ kg^{-1}. A population-based study showed similar results, with a 1.72-fold higher caffeine clearance in heavy smokers (≥20 cigarettes per day) compared with nonsmokers.[8] This suggests that CYP1A2 induction in smokers is mediated predominantly by the current exposure to components of cigarette smoke and not by substances released from tar deposited in the lung.

The transferability of our findings for pharmacotherapy with other CYP1A2 substrates is apparent from the comparison to clozapine, olanzapine, and theophylline. These drugs have a narrow therapeutic range, and indeed adverse drug reactions have been observed in connection with elevated plasma concentrations after smoking cessation. Clozapine disposition covaries with caffeine elimination, indicating a significant relationship between CYP1A2 activity and clozapine clearance.[2] CYP1A2 activity as measured by a caffeine test significantly contributed to clozapine steady-state plasma concentrations ($r_s = -0.87$, $P < .01$),[18] and a very high activity of CYP1A2 could be one reason for nonresponse to clozapine as a result of rapid metabolism.[19,20] Likewise, olanzapine disposition was significantly correlated with CYP1A2 activity as measured by various caffeine metabolic ratios.[21] For the metabolism of theophylline, the role of CYP1A2 has been investigated extensively.[22]

The magnitude of change observed in CYP1A2 activity on smoking cessation corresponds well to differences reported between smokers and nonsmokers with regard to clozapine pharmacokinetics. In a study conducted in 11 psychiatric patients allowed to smoke up to 14 cigarettes per day, mean plasma levels of clozapine increased by 57.4% on implementation of a hospital-wide nonsmoking policy.[12] A 1.5-fold clozapine dose reduction soon after smoking cessation has been proposed in a predictive model,[23] and a difference

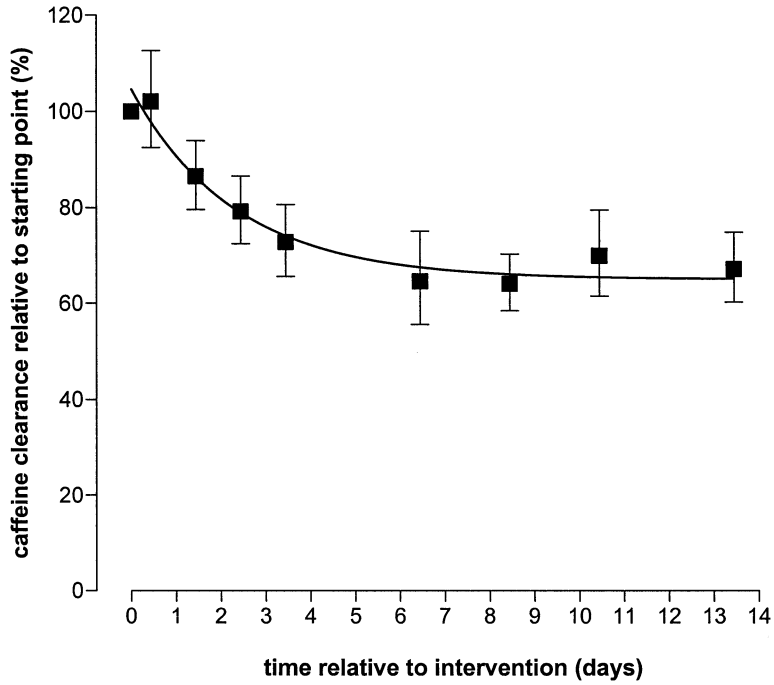

Fig 2. Time course of caffeine clearance after the intervention of smoking cessation. Points are geometric means and 95% confidence intervals based on log observed values (Fig 1). The geometric mean of individual caffeine clearance before intervention (denoted as time 0) was defined as 100%. The *line* represents the mean curve for the model fitted to the data by nonlinear regression analysis (see Methods section).

Table I. Data resulting from nonlinear regression analysis according to equation 2 (see Methods section)

	CI_{start} ($mL \cdot min^{-1} \cdot kg^{-1}$)	CI_{end} ($mL \cdot min^{-1} \cdot kg^{-1}$)	*Relative change (%)*	k_{CYP1A2} (h^{-1})	$t_{1/2}$ *of CYP1A2 (h)*
Subject No.					
1	2.04	1.29	36.6	0.0161	43.2
2	1.91	1.38	27.7	0.0149	46.5
3	2.57	1.94	24.4	0.0160	43.5
4	2.90	2.01	30.8	0.0048	143.7
5	4.66	2.79	40.1	0.0300	23.1
6	2.93	1.91	34.8	0.0270	25.7
7	1.64	1.15	30.1	0.0324	21.4
8	3.83	2.17	43.3	0.0178	38.9
9	1.84	1.25	32.1	0.0360	19.3
10	2.09	1.07	48.6	0.0169	41.0
11	2.23	0.93	58.4	0.0170	40.7
12	2.39	1.48	38.2	0.0125	55.4
Minimum	1.64	0.93	24.4	0.0048	19.3
Maximum	4.66	2.79	58.4	0.0360	143.7
Geometric mean	2.47	1.53	36.1	0.0179	38.6
95% CI based on log data	2.03–3.00	1.24–1.89	30.9–42.2	0.0128–0.0253	27.4–54.4

CI_{start}, Caffeine clearance before intervention of smoking cessation; CI_{end}, caffeine clearance when new steady state was reached after intervention, relative change, difference between starting and end values relative to starting point; k_{CYP1A2}, CYP1A2 activity change rate constant; $t_{1/2}$ of CYP1A2, half-life of CYP1A2 activity change; CI, confidence interval.

between smokers (≥15 cigarettes per day) and nonsmokers in clozapine maintenance doses needed to reach a given plasma concentration of approximately 50% has been found.[24] For theophylline, abstinence from smoking for 1 week resulted in a 37.6% decrease in clearance.[25]

This study, to our knowledge, is the first to systematically examine the time course of CYP1A2 activity in humans on abolition of enzyme induction. Through emerging adverse reactions to olanzapine or clozapine, case reports suggest that relevant symptoms can be perceived after as little as 4 days, after 14 days, or not until 1 month after smoking cessation.[11,13] This is in line with our finding that a new steady state of CYP1A2 activity on smoking cessation is reached roughly within a week, with the fact that new clozapine steady state after a dosage increase is reached within 10 days taken into account.[26] In the few case reports in which clozapine plasma concentrations have actually been measured on the occurrence of adverse drug reactions after smoking cessation, very high values of 1328 ng/mL[13] and 3066 ng/mL[12] have been found (the clinical target range is 250-400 ng/mL[27]). These data correspond to the extent of dose reduction required in other cases.[9,11] Under conditions of (relative) overdosing, the pharmacokinetics of clozapine becomes nonlinear because of saturation of norclozapine formation.[28,29] In addition, a gradual buildup of plasma concentrations or the reported development of tolerance to elevated plasma levels[30] might explain the long time lag from smoking cessation to onset of symptoms and the excessively high clozapine concentrations seen in some patients. Another possible explanation is the variation in CYP1A2 half-life to reach a new steady state according to the model (Table I).

The short mean half-life of CYP1A2 activity of 38.6 hours after smoking cessation suggests that the dose of CYP1A2 substrates with a narrow therapeutic range should be adjusted immediately after a change in smoking habits. Predicting the individual dose reduction required, however, is a challenging task. The number of cigarettes smoked per day[8] and other factors also influence the extent of CYP1A2 induction,[31,32] and concurrent medications may further alter CYP1A2-mediated drug metabolism. On the basis of our data, as a rule of thumb, we propose a stepwise daily dose reduction for CYP1A2 substrates of approximately 10% until the fourth day after smoking cessation. This adjustment slightly overcorrects the mean decrease in clearance to be on the safe side (see end of Results section) and of course does not take individual variation into account; it should, therefore, be accompanied by therapeutic drug monitoring.

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Both authors have no conflict of interest to declare.

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