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Influence of Age and Consumption of Tobacco, Alcohol and Caffeine on Antipyrine Clearance

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1 Antipyrine clearance and average daily consumption of tobacco, alcohol and coffee/tea were determined in 303 healthy men.
2 The antipyrine clearance was positively correlated with the consumption of tobacco ($r = 0.24$; $P < 0.0001$) and coffee/tea ($r = 0.18$; $P < 0.001$), and negatively with age ($r = -0.14$; $P < 0.05$) and the alcohol consumption ($r = -0.13$; $P < 0.05$).
3 The multiple regression coefficients suggested an increase in antipyrine clearance of 0.8% per daily cigarette or cup of tea and 1.4% per daily cup of coffee; the decrease per daily drink or year of age was 2.8% or 0.4%, respectively.

Introduction

The influence of environmental factors on hepatic drug metabolism can be assessed by means of the widely used probe, antipyrine.[1–3] Recently, we reported that the antipyrine clearance correlated positively with the self-reported daily consumption of caffeine and tobacco and negatively with age and the consumption of alcohol in 119 healthy subjects most of whom received concomitant metronidazole and/or oxazepam.[4] The negative association of the antipyrine clearance with age and the positive effect of smoking are well known.[5–8] However, in previous cross-sectional studies no significant independent correlations between alcohol and caffeine consumption and antipyrine clearance have been found.[5,7] One longitudinal study showed a decrease in antipyrine half-life after alcohol ingestion for 3 weeks,[9] whereas another study showed no significant effect on the antipyrine clearance of ingestion of caffeine or alcohol for 7 days.[10] Accordingly, we found it relevant to reinvestigate the influence of the consumption of tobacco, alcohol and caffeine on the rate of antipyrine elimination in a large population without concomitant drug administration.

Subjects and methods

The subjects were 303 healthy male office and factory workers and air force personnel, who participated in a series of previous studies on the influence of the working environment on the clearance of antipyrine.[2,11] In all subjects the antipyrine clearance was determined by the one-sample saliva method with sampling 24 h after ingestion of 1 g as previously described.[12] Salivary concentrations of antipyrine were determined by GC[13] or HPLC.[14] All antipyrine clearance measurements in this study were carried out in the end of a vacation in order to avoid influence from the working environment. None of the subjects took drugs regularly or reported intake of any drug for at least 1 week prior to the clearance determination. All subjects filled in identical questionnaires concerning their average daily smoking of tobacco in terms of number of cigarettes, cigars, cheroots or pipes and ingestion of drink equivalents (i.e. 10 g pure alcohol) and cups of coffee and tea. All tobacco containing items smoked were considered equivalent and counted as cigarettes. The subjects also stated their alcohol ingestion on the day before the antipyrine test. The consumption of caffeine was estimated as the coffee/tea index calculated as the number of cups of coffee plus 0.6 times the number of cups of tea.

Pearson product moment and Spearman rank correlation matrices were calculated for the recorded variables. Partial correlations between the antipyrine clearance and each factor controlling for the effect of the other factors were investigated by parametric methods. An expression of the influence of the recorded factors on the antipyrine clearance was calculated by least squares backwards multiple regression. P values less than 0.05 were considered statistically significant.

Results

The demographic characteristics and the self-reported daily consumption of stimulants of the 303 subjects are summarized in Table 1. The correlation matrices of all recorded variables are shown in Table 2. The Pearson product moment (below diagonal) and Spearman rank (above diagonal) correlation coefficients were almost identical. The average daily consumption of tobacco and coffee/tea was positively correlated and age and daily consumption of alcohol were negatively correlated with antipyrine clearance ($P < 0.05$). As several of the factors correlated with each other, partial correlation coefficients between the antipyrine clearance and each factor controlling for the linear effect of the others were calculated. This did not change the magnitude or statistical significance of the associations. The multiple regression equation predicting the antipyrine clearance was:

$$CL = 60 + 0.47 \times \text{no. of cigarettes} + 0.81 \times \text{coffee/tea index} - 1.70 \times \text{no. of drinks} - 0.25 \times \text{age}$$

The regression coefficients suggested that the antipyrine clearance was increased by 0.8% (0.4–1.2%; 95% confidence limits) per daily smoked cigarette or cup of tea and 1.4% (0.6%–2.1%) per daily cup of coffee, whereas the negative influence corresponded to 2.8% (1%–4.6%) per daily drink and 0.4% (0.1%–0.7%) per year of age. Fifteen per cent of the total variation was explained by the regression model.

Alcohol consumption and antipyrine clearance correlated significantly in the 185 smoking subjects ($r = -0.20$, $P < 0.01$), but not in the non-smokers ($r = -0.10$, $P < 0.25$).

Discussion

In a population of 303 healthy male factory and office workers and air force personnel, age and the self-reported average daily consumption of tobacco, alcohol and coffee and tea were found to be significant independent predictors of the clearance of antipyrine. The correlations were positive for consumption of tobacco and coffee/tea and negative for age and

Table 1 Demographic characteristics and self-reported average daily consumption of stimulants and antipyrine clearance (CL) in 303 male factory and office workers and air force personnel

	Age (year)	*Body weight (kg)*	*Height (cm)*	*Consumption of Tobacco (no. of cigarettes)*	*Alcohol (daily no. of drinks)*	*Alcohol[a] (yesterdays no.) of drinks)*	*Coffee/tea (index[b])*	*CL (ml/min)*
Mean	37	77	176	9.8	1.7	1.9	6.6	57
s.d.	10	10	11	9.0	1.7	2.6	4.1	17
Range	(18–64)	(49–106)	(155–199)	(0–40)	(0–11)	(0–20)	(0–23)	(21–117)

[a] Number of drinks (10 g alcohol) ingested the day before the antipyrine test.
[b] Index = no of cups of coffee + 0.6 × no of cups of tea.

Table 2. Correlation matrices of age, body weight (BW), height (BH), the average daily consumption of tobacco, alcohol (alc. daily) and the alcohol ingestion the day before the test (alc. yes.) and the clearance of antipyrine (CL) in 303 male subjects

	Age	*BW*	*BH*	*Tobacco*	*Alc. daily*	*Alc. yes.*	*Coffee/tea*	*CL*
Age	–	0.12*	−0.23§	0.01	−0.08	0.11	0.06	−0.11
BW	0.10*	–	0.47§	0.02	0.00	−0.10	0.10	0.02
BH	−0.11*	0.33§	–	−0.01	−0.07	−0.12*	0.02	0.05
Tobacco	0.01	0.02	−0.08	–	0.05	0.09	0.28*	0.32*
Alc. daily	−0.03	0.01	0.04	0.15*	–	0.47*	−0.07	−0.14*
Alc. yes.	0.07	−0.06	−0.06	0.17*	0.53*	–	−0.10	−0.10
Coffee/tea	0.01	0.07	0.05	0.27§	−0.07	−0.07	–	0.27*
CL	−0.13*	0.02	0.02	0.26§	−0.14*	−0.11	0.26*	–
CL[a]	−0.14*	0.01	0.01	0.24§	−0.13*	−0.05	0.18†	–

Pearson product moment correlation coefficients are below the diagonal and Spearman rank correlation coefficents are above: * $P < 0.05$; † $P < 0.005$; § $P < 0.0001$.
[a] Partial correlation coefficients controlling the effect of the other independent variables.

alcohol consumption. Although some variables probably deviated form the normal distribution, correlation coefficients were practically identical using parametric or non-parametric statistical methods.

Previously, we have reported almost identical correlation coefficients in a population sample of 119 subjects including 7 women.[4] However, most of these subjects received one or two other drug(s) concomitant with the antipyrine test dose. Thus, the confirmation of the correlations in a more homogenous and drug-free population was wanted. The results of the present and our previous study are in complete agreement and suggest that smoking and caffeine consumption have an enhancing effect and consumption of alcohol and advancing age have a reducing effect on the rate of antipyrine elimination. The influences estimated from the multiple regression coefficients amounted to a 1% increase in clearance per daily smoked cigarette or ingested cup of coffee or tea and a 3 and 0.4% decrease per daily drink or year of age, respectively. It should be borne in mind that this regression model only explained 15% of the total variation. The lack of correlation between antipyrine clearance and alcohol ingestion the day before the test supports a non-acute effect.[15] Our two investigations also confirm the applicability of the one-sample method for large population studies, provided the influence of errors in the estimate of the volume of distribution are minimized by late sampling.[3]

The inducing effect of smoking and the negative effect of age on the rate of antipyrine elimination are well known.[5–8] The previous cross-sectional studies of the relations between the consumption of coffee and alcohol and the antipyrine clearance have not shown significant independent associations.[3,5] In one longitudinal study of 6 prisoners, who received alcohol 1 ml kg^{-1} d^{-1} for 21 days, the mean half-life of antipyrine decreased by 22%.[9] However, in that particular study clearance was not determined. Consequently, it cannot be excluded that the decline in antipyrine half-life was caused by an alcohol-induced decrease in the volume of distribution, indicated by an increase in the time zero intercept of the log-plasma concentration–time curve in 5 of the 6 subjects in that study.[9] Another important unknown factor was the smoking habits of the subjects before and during that study. In another longitudinal study of 10 non-smoking subjects receiving 5 drinks per day for 1 week the antipyrine clearance was 0.89 times the control value on average, although not significantly changed.[10] After daily ingestion of 6 cups of coffee for 7 days in the same study the antipyrine clearance was 1.06 times the control value, but not altered to a statistically significant extent.[10] Those data are compatible with the multiple regression coefficients of the present study.

At least three different cytochrome P-450 isozymes are involved in the metabolism of antipyrine and each may be affected differently by alcohol, possibly explaining some of the diverging results discussed here. In the present study the significant negative correlation between consumption of alcohol and antipyrine clearance was confined to the smoking subjects, suggesting that daily alcohol intake may primarily inhibit particular hepatic enzymes induced by tobacco smoke content. In support, the clearance of caffeine decreased 0.64-fold during alcohol treatment for 7 days.[10] Antipyrine and caffeine are thought to share some metabolic enzymes, presumably inducible by polyaromatic hydrocarbons.[16] Very recently the effect of age on the metabolism of antipyrine has been shown to be differential on the formation rate of each metabolite.[17] Tobacco smoking has not yet been demonstrated to induce the formation of antipyrine metabolites differentially.[8] More studies concerning the influence of daily use of stimulants on the metabolism of antipyrine with the determination of the metabolite profile, are needed to determine the effect on different cytochrome P-450 isozymes.

In conclusion the present study has demonstrated a significant positive association between the antipyrine clearance and the consumption of tobacco and caffeine and a negative association between the clearance and the consumption of alcohol and age.

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