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THE EFFECT OF SMOKING ON CAFFEINE ELIMINATION: IMPLICATIONS FOR ITS USE AS A SEMIQUANTITATIVE TEST OF LIVER FUNCTION

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SUMMARY

1. The effects of caffeine ingestion and cigarette smoking on caffeine and antipyrine pharmacokinetics were studied using normal subjects as their own controls before and after cessation of smoking in an attempt to minimize genetic and other environmental influences.

2. Moderate caffeine ingestion had no inducing effect on caffeine or antipyrine clearance.

3. Cessation of cigarette smoking significantly reduced clearance of caffeine and antipyrine.

4. These results demonstrate that cigarette smoking significantly affects caffeine pharmacokinetics and this may contribute to the variable results for caffeine kinetics found in patients with liver disease.

Key words: caffeine, drug metabolism, liver function, smoking.

INTRODUCTION

The need for quantitative tests of liver function has become increasingly important with the advent of liver transplantation programmes. Accurate assessment of total liver functional reserve and prognosis is one of the most important factors determining the timing and need for transplantation. Previously proposed quantitative tests, including galactose elimination capacity, aminopyrine breath testing and antipyrine plasma clearance, have been limited by problems of specificity, sensitivity and complexity of implementation (Tygstrup 1966; Andreasen *et al.* 1974; Bircher *et al.* 1976).

Recent reports have suggested that the estimation of caffeine pharmacokinetic parameters may provide a simple, sensitive and quantitative method of measuring functional hepatic mass (Desmond *et al.* 1980; Renner *et al.* 1984; Wahllander *et al.* 1985; Wang *et al.* 1985). Caffeine is commonly consumed and relatively non-toxic and the pharmacokinetics have been well

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characterized. After oral administration, it is rapidly absorbed with 100% bioavailability, and is metabolized largely by hepatic demethylation (Bonati *et al.* 1982). In healthy subjects, caffeine elimination is by apparent first order kinetics over a range of doses.

Early reports showed that caffeine clearance was impaired markedly in patients with cirrhosis (Desmond *et al.* 1980; Wang *et al.* 1985). However, subsequent studies have documented a relatively poor correlation between caffeine kinetics and other markers of disease activity (Mooney *et al.* 1984; Khan 1987). In view of the influence of a range of environmental factors on hepatic drug metabolism (Rubin *et al.* 1970; Parsons & Neims 1978; George *et al.* 1986), it is possible that this variation in caffeine pharmacokinetics was attributable to factors other than liver disease.

In a previous report, we demonstrated a strong inhibitory effect of alcohol consumption on caffeine, but not antipyrine, kinetics (George *et al.* 1986). In the present paper, we report the effects of cigarette smoking on clearance of caffeine and compare the effects on antipyrine kinetics, an alternate measure of functional hepatic mass.

METHODS

Materials

Pure caffeine, antipyrine and 3-isobutyl-1-methyl xanthine (3-IBMX) were obtained from Sigma Chemical Co., St Louis, USA and phenacetin from BDH Chemicals, England. Methanol and chloroform were HPLC grade from Waters Associates, Australia.

Subjects

Sixteen healthy subjects volunteered to participate in the study. They smoked a minimum of 10 cigarettes per day and were on no medications. Eight were successful in giving up smoking and they have been included in this study. After written informed consent was obtained, a full blood count and multiple biochemical analyses were performed and the intake of tobacco and caffeine was documented (Table 1).

Caffeine and antipyrine kinetics were performed at each of the following stages.

Phase I While smoking a minimum of 10 cigarettes per day and abstaining from alcohol and caffeine-containing foods, beverages or drugs for 5 days.

Phase II While smoking a minimum of 10 cigarettes per day and abstaining from alcohol as before, but after caffeine loading. This was achieved by consuming a minimum of six cups of coffee

Table 1. Relevant data on patients studied

Subject	Sex	Age	Weight (kg)	Daily caffeine consumption (mg)	No. of cigarettes per day
DM	M	24	85	420	15
JL	M	45	99	140	25
SF	M	19	105	110	15
JS	M	23	80	280	15
BW	M	29	60	560	25
SP	M	28	60	1000	25
AC	M	22	60	140	20
RB	F	24	65	350	15

per day for 7 days. Subjects abstained from caffeine-containing compounds for 2 days prior to the tests.

Phase III Having abstained from tobacco products for a minimum of 30 days and from alcohol- and caffeine-containing foods, beverages and drugs for 5 days.

Phase IV Having abstained from tobacco products and alcohol as before, but after caffeine loading as in Phase II above.

Caffeine kinetic studies were performed on the first day and antipyrine on the following day. The subjects were fasted from the midnight prior to a study.

Caffeine (110 mg) was added to 1.5 g of commercially available decaffeinated coffee (caffeine content 1.3 mg) which was ingested on the first day. Serial blood samples were collected through an indwelling cannula at 0 (zero time, fasting) 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 10.0, and 24 h after administration. Serum was then separated and stored at −20°C for analysis.

On the second day, pure antipyrine (10 mg/kg body weight) was administered in 100 ml of orange juice and blood samples collected as above.

Analytical methods

Caffeine and antipyrine assays were performed as described previously (George *et al.* 1986).

Following extraction of 0.5 ml serum in an acidic medium with 3 ml chloroform in the presence of 3-IBMX as internal standard, serum caffeine was determined using HPLC with a 30 cm × 0.4 cm μ Bondapak C18 column (Waters) and quantitated using known amounts of standards. Phenacetin was used as the internal standard for antipyrine assays and extraction performed in an alkaline medium using 5 N NaOH (Roberts *et al.* 1981). All serum samples and standards were assayed in duplicate.

Calculations

The data were fitted to a pharmacokinetic model on a computer, which provided elimination rate constants (k) by log-linear regression analysis of serum caffeine concentration versus time. Half-life ($t_{1/2}$) was calculated as ln 2/k and clearance (Cl) as dose/area under the curve (AUC). AUC was calculated by the trapezoidal rule up to the last determined concentration and then extrapolated to infinity by dividing the last determined concentration by k. Results were expressed as means and standard deviation (s.d.). Statistical comparison between groups was performed using Student's paired *t*-test.

RESULTS

The pharmacokinetic data for caffeine and antipyrine are presented in Table 2. Caffeine loading did not significantly affect either of the kinetic parameters. However, a significant decrease in caffeine clearance was observed on cessation of smoking ($P<0.001$). The range of caffeine clearances was very narrow in the non-smoking phase being 1.15–2.85 versus 1.79–5.3 ml/min per kg in the smoking phase. The mean prolongation of caffeine $t_{1/2}$ was 29% ($P<0.0001$) while Cl was diminished by 36% ($P<0.0005$). Antipyrine $t_{1/2}$ was prolonged by 16% ($P<0.001$) and Cl diminished by 24% ($P<0.002$).

Table 2. Serum caffeine and antipyrine kinetics

Phase ($n=8$)	$t_{½}$ (h)		Clearance (ml/min per kg)	
	Caffeine	Antipyrine	Caffeine	Antipyrine
I	2.83 ± 0.87 (1.17–3.68)	8.19 ± 1.81 (5.46–10.65)	3.76 ± 1.22 (1.79–5.3)	1.34 ± 0.40 (0.95–2.02)
II	2.51 ± 0.85 (1.20–3.66)	8.53 ± 1.80 (5.63–10.57)	4.03 ± 1.40 (1.75–6.2)	1.29 ± 0.41 (0.95–1.96)
III	3.98 ± 0.91* (2.98–5.6)	9.77 ± 2.05** (6.43–12.57)	2.44 ± 0.47† (1.15–2.85)	1.02 ± 0.33†† (0.69–1.75)
IV	4.40 ± 1.38 (3.00–6.50)	9.35 ± 1.83 (6.43–11.97)	2.21 ± 0.70 (1.00–3.11)	1.05 ± 0.32 (0.70–1.75)

Results expressed as mean ± s.d.; range in parentheses.
Significance (I vs III): *$P<0.0001$; **$P<0.001$; †$P<0.0005$; ††$P<0.002$.

DISCUSSION

This study has shown that cigarette smoking significantly affects both caffeine and antipyrine pharmacokinetics. In all subjects studied, cessation of smoking produced a prolongation of caffeine and antipyrine half-lives and a decrease in caffeine and antipyrine clearance, although the magnitude of change was not predictable for any individual subject. This is consistent with earlier reports showing enhancement of hepatic drug metabolism by cigarette smoking (Hart *et al.* 1976; Vaughan *et al.* 1976; Parsons & Neims 1978; Grygiel & Birkett 1981; Grech-Belanger *et al.* 1985). Parsons and Neims (1978) reported a 50% reduction in caffeine half-life and increased caffeine clearance in 13 healthy smokers compared with a separate control group of non-smokers. The present study has confirmed this observation using subjects as their own controls, which eliminates potential interindividual, genetic and environmental factors which may complicate pharmacokinetic analysis. In contrast, regular caffeine consumption for a 7 day period did not affect either caffeine or antipyrine kinetics in this study. It is interesting to note that cessation of smoking also produced a decrease in the interindividual variation in caffeine clearance.

The mechanism by which cigarette smoking alters caffeine and antipyrine metabolism has not been addressed in this study but it presumably acts by induction of hepatic drug metabolizing enzymes such as aryl hydrocarbon hydroxylase as a result of the action of polycyclic hydrocarbons (e.g. benzpyrene) present in cigarette smoke (Parsons & Neims 1978). However, other components of cigarette smoke cannot be excluded as contributing agents.

We have previously documented that ethanol consumption significantly prolongs caffeine half-life and reduces caffeine clearance (George *et al.* 1986). Thus a number of common environmental agents may influence caffeine metabolism in a way that is not easily predictable.

Caffeine elimination is reduced in patients with liver failure (Statland *et al.* 1976; Desmond *et al.* 1980; Branch 1982; Renner *et al.* 1984) and this has led to the suggestion that plasma caffeine levels may provide a useful index of functional liver cell mass somewhat akin to the serum creatinine concentration for renal function (Wahllander *et al.* 1985; Wang *et al.* 1985). However, since cigarette smoking and alcohol consumption are common habits among patients with liver disease, the results of the present study suggest that random assessment of caffeine or antipyrine metabolism may be unreliable as prognostic tests of liver function, unless corrected for tobacco and ethanol consumption. This may be more readily accomplished in the context of long-term follow-up of selected patients rather than as a screening test for significant liver dysfunction.

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