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Caffeine renal clearance and urine caffeine concentrations during steady state dosing. Implications for monitoring caffeine intake during sports events

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1 Relationships between the plasma and urine concentrations and clearances of caffeine over successive dosage intervals at steady-state were investigated in six healthy volunteers administered caffeine, 150 mg 8 hourly for 6 days.
2 There was marked inter-individual variability in the urine (15.9-fold range) and steady-state plasma (8.1-fold range) concentrations of caffeine.
3 Urine caffeine concentrations were similar to those in plasma, with mean ratios (plasma:urine) ranging from 1.10 to 1.74. There was a good correlation ($r = 0.93$, $P < 0.01$) between caffeine urine and plasma concentrations.
4 There was a good correlation between caffeine renal clearance and urine flow rate ($r = 0.89$, $P < 0.01$). Caffeine renal clearance was not significantly different from the product of f_u and urine flow rate, where f_u is the fraction of caffeine unbound in plasma. Urine caffeine concentration and urine flow rate were not correlated ($r = 0.14$, $P > 0.05$).
5 The results indicate that caffeine is reabsorbed from the renal tubule to equilibrium with unbound caffeine in plasma.
6 A regulatory urine caffeine concentration limit of 12 mg l^{-1} may be exceeded by some individuals with coffee intake in the range 3 to 6 cups per day.

Keywords caffeine plasma concentration urine concentration sports monitoring

Introduction

Caffeine intake by athletes during international sporting events is monitored by urine caffeine concentrations with the current limit being set at 12 mg l^{-1}. The rationale for this limit is not clear as few data correlating blood or plasma caffeine concentrations with effects on sports performance are available. Further, there are little or no published data correlating urine caffeine concentrations with blood concentrations and/or caffeine intake. Such data are necessary to assess what level of intake is 'safe' in relation to the urine concentration limit.

Caffeine is a highly metabolised drug with only about 0.5% to 3% being excreted unchanged in urine (Bonati *et al.*, 1982; Newton *et al.*, 1981; Tang-Liu *et al.*, 1983). Thus, for a given intake rate the average steady state blood caffeine concentration will depend on caffeine metabolic clearance. Typically, this shows an inter-individual variability of the order of 3- to 15-fold (Lelo *et al.*, 1986a,b,c; May *et al.*, 1982; Parsons & Neims, 1978). The urine caffeine concentration could be expected to show greater variability as this parameter will depend on blood caffeine concentration, caffeine renal clearance and urine flow rate.

This study was designed to assess the urine caffeine concentrations achieved during moderate steady state caffeine intake in a group of six healthy young volunteers. The intra- and inter-individual variability in plasma and urine concentrations were assessed, as were the effects of urine flow rate on caffeine renal clearance and urine caffeine concentrations.

Methods

The subjects were six healthy volunteers, three males and three females, aged 21.0 ± 0.9 years (range 20 to 22

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years) and weighing 63 ± 11 kg (range 50 to 76 kg). All were nonsmokers. Subjects abstained from all methylxanthine containing foods and beverages during the entire period of the study. Compliance with this requirement was assessed by questioning at each presentation for blood sampling or urine delivery. Each subject took 150 mg caffeine BP in hard gelatin capsules 8 hourly at 07.00, 15.00 and 23.00 h for 6 days. Compliance was assessed by capsule count and by a diary card recording drug intake. For the purposes of another study each subject was given a single dose of allopurinol 600 mg at 07.00 h on day 4 of the study.

From day 3 of the study, when steady state had been reached, urine was collected over each 8 h dosing interval, giving a total of 11 urine samples for each subject. On days 4, 5 and 6, blood samples were taken at 11.00 h and 19.00 h, the midpoints of the morning and afternoon dosing intervals, respectively. One data point from subject 3 was omitted due to a missed urine collection.

Plasma was separated by centrifugation and stored at −20° C. Urine volume was measured by weighing and 10 ml aliquots were stored at −20° C. Caffeine concentrations in plasma and urine were measured by a specific high performance liquid chromatographic procedure (Foenander *et al.*, 1980).

Caffeine renal clearance (CL_R) was calculated as the caffeine excretion rate divided by the midpoint plasma caffeine concentration, and caffeine plasma clearance (CLp) as the dose rate (18.75 mg h^{-1}) divided by the plasma caffeine concentration at the midpoint of the dosing interval. If tubular reabsorption of caffeine continues until equilibrium with unbound caffeine in plasma is reached, then $CL_R = fu \times$ urine flow rate. An average fraction unbound (fu) of 0.7 (Lelo *et al.*, 1986b) was used in assessing this relationship for caffeine. Results are expressed as mean ± s.d. Correlations between parameters were assessed by linear regression analysis.

Written informed consent to the study was given by each subject and the study was approved by the Drug and Therapeutics Advisory Committee and the Committee on Clinical Investigation of the Flinders Medical Centre.

Results

There was no effect of the allopurinol dose on the urine or plasma caffeine concentrations which showed no trend over the period of study. Table 1 shows the plasma and urine caffeine concentrations, the plasma/urine concentration ratios and the caffeine renal and plasma clearances for each subject. Individual mean plasma caffeine concentrations at steady state, and therefore the estimated caffeine plasma clearances, varied over a 5-fold range, while the intra-individual variability ranged from 1.1- to 3.3-fold in different individuals. Urine caffeine concentrations were similar to those in plasma with individual mean plasma:urine concentration ratios ranging from 1.10 to 1.74, and there was a good correlation (Figure 1) between urine and plasma caffeine concentrations ($r = 0.93, P < 0.01$). However,

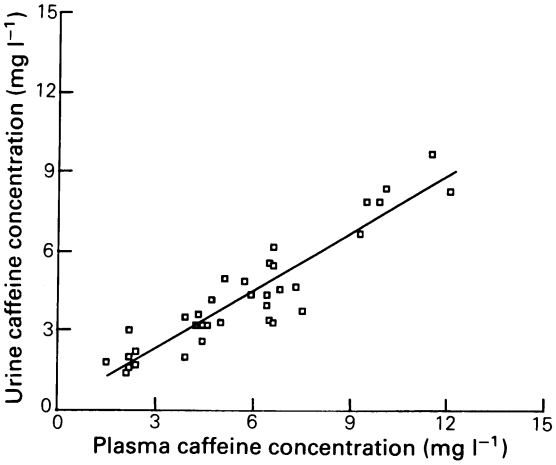

Figure 1 Correlation between plasma and urine caffeine concentrations ($n = 35$). $y = 0.16 + 0.73x$, $r = 0.93$, $P < 0.001$.

Table 1 Plasma and urine caffeine concentrations and caffeine pharmacokinetic parameters

Subject	*Weight (kg)*	*Cu*[a] *(mg l^{-1})*	*Cp*[b] *(mg l^{-1})*	*Cp/Cu*[c]	*CL_R*[b] *(ml min^{-1})*	*CLp*[b] *(ml min^{-1})*
1	76	1.6 ± 0.5 (0.7–2.2)	2.1 ± 0.3 (1.5–2.4)	1.10 ± 0.28 (0.71–1.50)	0.64 ± 0.20	150.3 ± 26.8
2	74	2.8 ± 0.6 (2.0–3.6)	4.2 ± 0.2 (3.9–4.4)	1.42 ± 0.30 (1.11–1.95)	0.50 ± 0.08	74.9 ± 3.9
3	55	4.3 ± 0.9 (3.0–5.6)	5.3 ± 0.8 (4.6–6.5)	1.18 ± 0.16 (0.86–1.44)	0.58 ± 0.18	58.3 ± 7.5
4	50	8.7 ± 1.3 (6.7–11.1)	10.4 ± 1.0 (9.3–12.1)	1.28 ± 0.11 (1.19–1.46)	0.55 ± 0.35	30.3 ± 2.9
5	54	5.1 ± 1.4 (3.0–7.7)	5.6 ± 1.7 (2.2–7.3)	1.23 ± 0.28 (0.73–1.55)	0.55 ± 0.23	65.8 ± 34.6
6	67	3.9 ± 0.5 (3.3–4.6)	6.7 ± 0.4 (6.4–7.5)	1.74 ± 0.23 (1.45–2.0)	1.01 ± 0.32	46.8 ± 2.5

[a]. Mean ± s.d. (range) of 11 values for each subject (10 for subject 3).
[b]. Mean ± s.d. (range) of 6 values for each subject (5 for subject 3).
[c]. Mean ± s.d. (range) of matched plasma and urine concentrations from each subject.

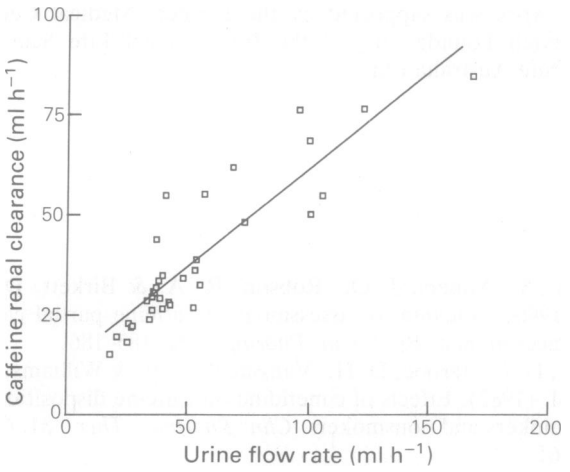

Figure 2 Correlation between caffeine renal clearance and urine flow rate (n = 35). y = 12.4 + 0.5x, r = 0.89, $P < 0.001$.

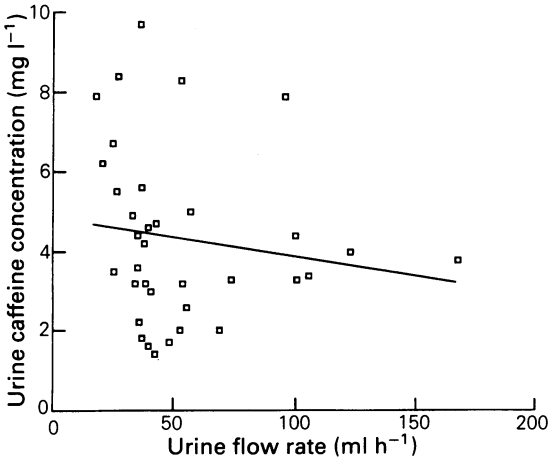

Figure 3 Correlation between caffeine concentration in urine and urine flow rate (n = 35). y = 4.8 + 0.01x, r = 0.15, $P > 0.05$.

even within individuals there was substantial variation in the plasma:urine concentration ratio (up to 2.0-fold). The intra- and inter-individual variability in urine caffeine concentrations were similar to those for plasma, with the overall range of urine caffeine concentrations being 0.7 mg l^{-1} to 11.1 mg l^{-1} (15.9-fold).

Renal caffeine clearance was low with between 0.4% to 2.1% of the dose being excreted unchanged over the dosage interval. There was a good correlation between caffeine renal clearance and urine flow rate (r = 0.89, $P < 0.01$; Figure 2), and mean caffeine CL_R (38.5 ± 18.2 ml h^{-1}) was not significantly different from fu × urine flow rate (37.3 ± 23.0 ml h^{-1}, n = 35, P = 0.5). As expected from the above, urine caffeine concentration and urine flow rate were not correlated (r = 0.15, $P > 0.05$; Figure 3).

Discussion

The steady state caffeine intake of the subjects in this study represents about five to six cups of average strength brewed coffee per day (Burg, 1975; Gilbert *et al.*, 1976; Lelo *et al.*, 1986a). However, the caffeine content of coffee varies widely depending on strength (caffeine concentration) and volume, so that as little as three to four cups per day could result in a similar intake of caffeine (Lelo *et al.*, 1986a). Despite this relatively modest intake, one of the subjects showed a urine caffeine concentration close to the international sporting limit of 12 mg l^{-1}. Even with this small and relatively homogeneous group of subjects, the overall variability in urine caffeine concentrations was 15.9-fold with a standard caffeine intake. In a more diverse population, the variability is likely to be even greater. Some individuals could well exceed the current regulatory limit with a coffee intake of about three to six cups of coffee per day, particularly if a urine sample was collected around a time of peak plasma caffeine concentration. Given the severe consequences of a single urine caffeine concentration above the regulatory limit, the latter should be set to allow for the extremes of the population in relation to caffeine pharmacokinetic parameters. Based on the present study, and on other studies of caffeine pharmacokinetics, a population variability of the order of 20-fold should be assumed.

The present study involved steady state caffeine intake. It can be calculated based on a caffeine volume of distribution of about 0.5 l kg^{-1} (Lelo *et al.*, 1986b; Newton *et al.*, 1981; Parsons & Neims, 1978), and the plasma:urine caffeine concentration ratio of about 1.3 found in this study, that a single dose of about 500 mg caffeine would give urine levels around 12 mg l^{-1}.

Although the plasma clearance values in this study were estimates based on single concentrations at the midpoint of the dosing interval, they are very similar to those reported by us and others (Lelo *et al.*, 1986b,c; May *et al.*, 1982; Newton *et al.*, 1981). It is acknowledged, however, that the use of a single plasma concentration at steady-state to estimate caffeine plasma and renal clearances may well have contributed to the variability (particularly intra-individual) in these parameters since the plasma concentration measured will be subject to the influence of absorption rate.

The low degree of excretion of unchanged drug is in agreement with previous reports (Bonati *et al.*, 1982; Newton *et al.*, 1981; Tang-Liu *et al.*, 1982). There was a high degree of correlation between caffeine CL_R and urine flow rate (r = 0.89, $P < 0.001$) which has also been found by other investigators (Newton *et al.*, 1981; Tang-Liu *et al.*, 1982). In this study, caffeine CL_R was not significantly different from fu × urine flow rate, indicating that, over the range of urine flow rates achieved, caffeine is reabsorbed in the renal tubule to equilibrium with unbound caffeine in plasma. This accounts for the high correlation between plasma and urine caffeine concentrations (Figure 1) and the lack of effect of urine flow rate on urine caffeine concentration (Figure 3).

In summary, the urine caffeine concentration is a measure of the unbound concentration of caffeine in plasma over a wide range of urine flow rates. For a given steady state caffeine intake, there is marked intra- and inter-individual variability in both urine and plasma caffeine concentrations, and the current regulatory limit for urine caffeine concentration in international sporting events is likely to place some individuals at risk after

only modest coffee intake. The limit needs to be revised, or athletes advised to limit their intake to the order of two to three cups of coffee per day or the equivalent in terms of caffeine intake.

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References

Bonati, M., Latini, R., Galletti, F., Young, J. F., Tognoni, G. & Garattini, S. (1982). Caffeine disposition after oral doses. *Clin. Pharmac. Ther.*, **32**, 98–106.

Burg, A. W. (1975). Effects of caffeine on the human system. *Tea Coffee Trade J.*, **88**, 40–42.

Foenander, T., Birkett, D. J., Miners, J. O. & Wing, L. M. H. (1980). The simultaneous determination of theophylline, theobromine and caffeine in plasma by high performance liquid chromatography. *Clin. Biochem.*, **13**, 132–134.

Gilbert, R. M., Marshman, J. A., Schwieder, M. and Berg, R. (1976). Caffeine content of beverages as consumed. *Can. med. Ass. J.*, **114**, 205–208.

Lelo, A., Birkett, D. J., Robson, R. A. & Miners, J. O. (1986b). Comparative pharmacokinetics of caffeine and its primary demethylated metabolites paraxanthine, theobromine and theophylline in man. *Br. J. clin. Pharmac.*, **22**, 177–182.

Lelo, A., Miners, J. O., Robson, R. A. & Birkett, D. J. (1986a). Assessment of caffeine exposure: caffeine content of beverages, caffeine intake, and plasma concentrations of methylxanthines. *Clin. Pharmac. Ther.*, **39**, 54–59.

Lelo, A., Miners, J. O., Robson, R. A. & Birkett, D. J. (1986c). Quantative assessment of caffeine partial clearances in man. *Br. J. clin. Pharmac.*, **22**, 183–186.

May, D. C., Jarboe, D. H., VanBakel, A. B. & Williams, W. M. (1982). Effects of cimetidine on caffeine disposition in smokers and nonsmokers. *Clin. Pharmac. Ther.*, **31**, 656–661.

Newton, R., Broughton, L. J., Lind, M. J., Morrison, P. J., Rogers, H. J. & Bradbrook, I. D. (1981). Plasma and salivary pharmacokinetics of caffeine in man. *Eur. J. clin. Pharmac.*, **21**, 45–52.

Parsons, M. D. & Neims, A. H. (1978). Effect of smoking on caffeine clearance. *Clin. Pharmac. Ther.*, **24**, 40–45.

Tang-Liu, D. D., Williams, R. L. & Riegelman, S. (1983). Disposition of caffeine and its metabolites in man. *J. Pharmac. exp. Ther.*, **224**, 180–185.

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