

Intra-individual variability of caffeine elimination in healthy subjects

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Abstract. Caffeine is a popular test substance for assessing the activity of hepatic drug metabolizing enzymes in vivo and in vitro. A correct estimation of the relative magnitudes of *intra*-individual and *inter*-individual variations in caffeine elimination is significant for the use of the elimination parameter of caffeine to characterize the biotransformation capacity of a specific form of cytochrome P-450 (1AII) in vivo. The purpose of this study is to demonstrate the magnitudes of fluctuation of caffeine-clearance and half-life as well as *inter*- and *intra*-individual comparison in 12 healthy male subjects. Compared to the high reproducibility of caffeine decay curves in each healthy male, caffeine elimination varied more extensively between subjects. The distribution of variance amounted to: *intra*-individual 21.4%, *inter*-individual 78.6%. The knowledge of variance provided precise evidence of the sample size, which is necessary to prove previously defined differences.

Key words: healthy man – caffeine kinetics – variability

Introduction

The kinetics of model drug substrates in vivo were used to assess endogenous and exogenous factors of drug-metabolizing enzyme activity or to determine polymorphism in drug metabolism [Park et al. 1987]. Its plasma clearance or the rate of appearance of a metabolite should be directly related to the activity of enzyme(s) responsible for metabolism.

Caffeine is used in man to characterize the biotransformation capacity of cytochrome P-450 (1AII) in vivo and in vitro [Balogh et al. 1990 and 1991, Fuhr et al. 1990 and 1991]. The decrease in caffeine clearance is closely related to the Child's classification [Holstege et al. 1989] of hepatic insufficiency. The compound is characterized by rapid and complete absorption [Bonati 1982, Blanchard and Sawers 1983] and lack of toxicity. However, disposition of the drug is subject of marked *inter*-individual variability, the coefficient of variation of elimination parameter is reported to be about 40% [Cheng et al. 1990, Balogh 1991]. There are not so many data on

intra-individual variability of caffeine elimination. In one study [Cheng et al. 1990], the *intra*-subject variability did not exceed 5% in each of the three healthy subjects. In contrast, Kalow et al. [1985] quoted unpublished data in which the *intra*-individual variation was about 16%.

The purpose of the present paper is to demonstrate the magnitude of *inter*- as well as *intra*-individual variability of caffeine clearance and elimination half-life in a considerable number of subjects. In a previous study, the effects of various quinolones on the pharmacokinetics of caffeine were investigated by *intra*-individual comparison of caffeine administration before and under quinolone intake [Harder et al. 1988].

Caffeine was repeatedly administered, in each subject six times before and after quinolone treatment.

Methods

The single dose kinetics of caffeine was investigated each time before the administration of specific quinolone in 12 healthy male volunteers (ages 24 to 39 years) and whose weight ranged from 65 kg to 100 kg. None had a history of serious illness, regular consumption of any medication, smoking, or of a chronic exposure to chemicals known to induce or inhibit hepatic drug metabolizing enzymes. Informed consent was obtained from the participants.

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A single oral dose of caffeine-citrate solution (220–230 mg caffeine base per dose, i.e. an equivalent to 3–4 cups of coffee) was given on day 1. Thereafter, the interaction was tested in a randomized design [Harder et al. 1988]. Caffeine elimination was assessed again after a two-week wash-out phase. Subjects received a

methylxanthine-free diet for 36 h before and 24 h after caffeine administration.

Serum caffeine concentrations were determined by HPLC. Pharmacokinetic parameters were derived from the plasma-concentration-time curve of the regression-line of the terminal slope

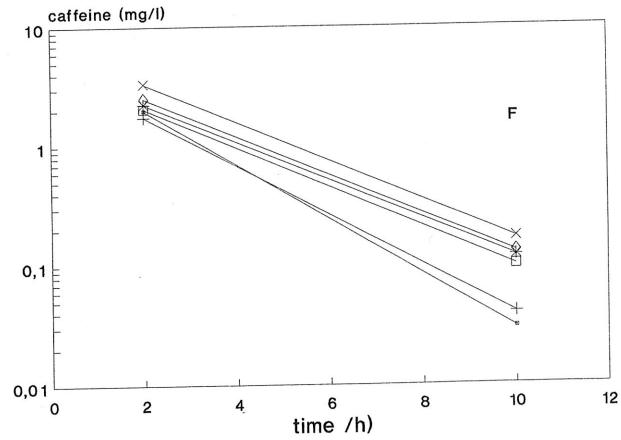
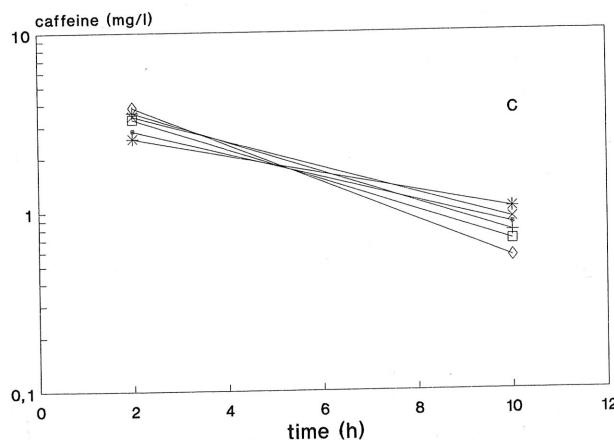
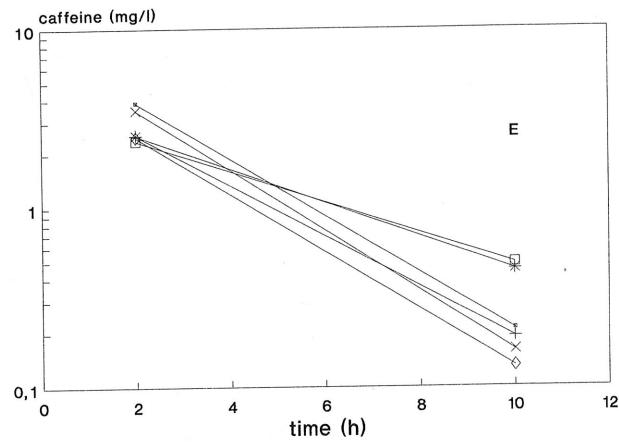
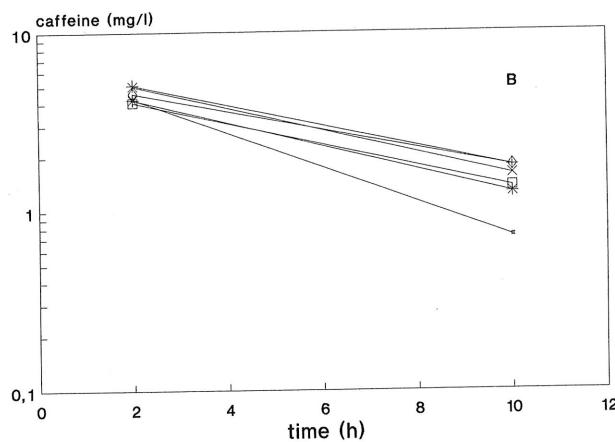
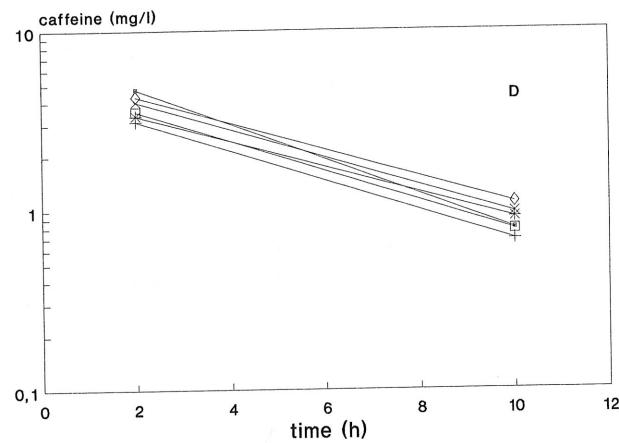
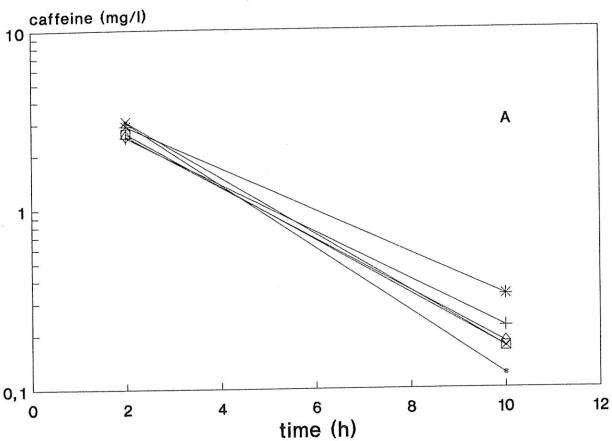


Abb. 1a-f

($t_{1/2}$; $CL_{tot} = aV_d \times k_{el}$; aV_d = dose/ C_0). To assess the *intra-* and *inter-individual* variability, the coefficients of variation (CV) and *intra-* and *inter-individual* portions within total variance [Adam et al. 1977, Fahrmeir and Hamerle 1984] were estimated (unbiased estimator) for the parameter CL_{tot} and $t_{1/2}$.

Results

Figure 1 shows individual slopes of caffeine decay curves obtained for all volunteers. The main observations in this study on *intra-individual* versus *inter-individual* variability in caffeine elimi-

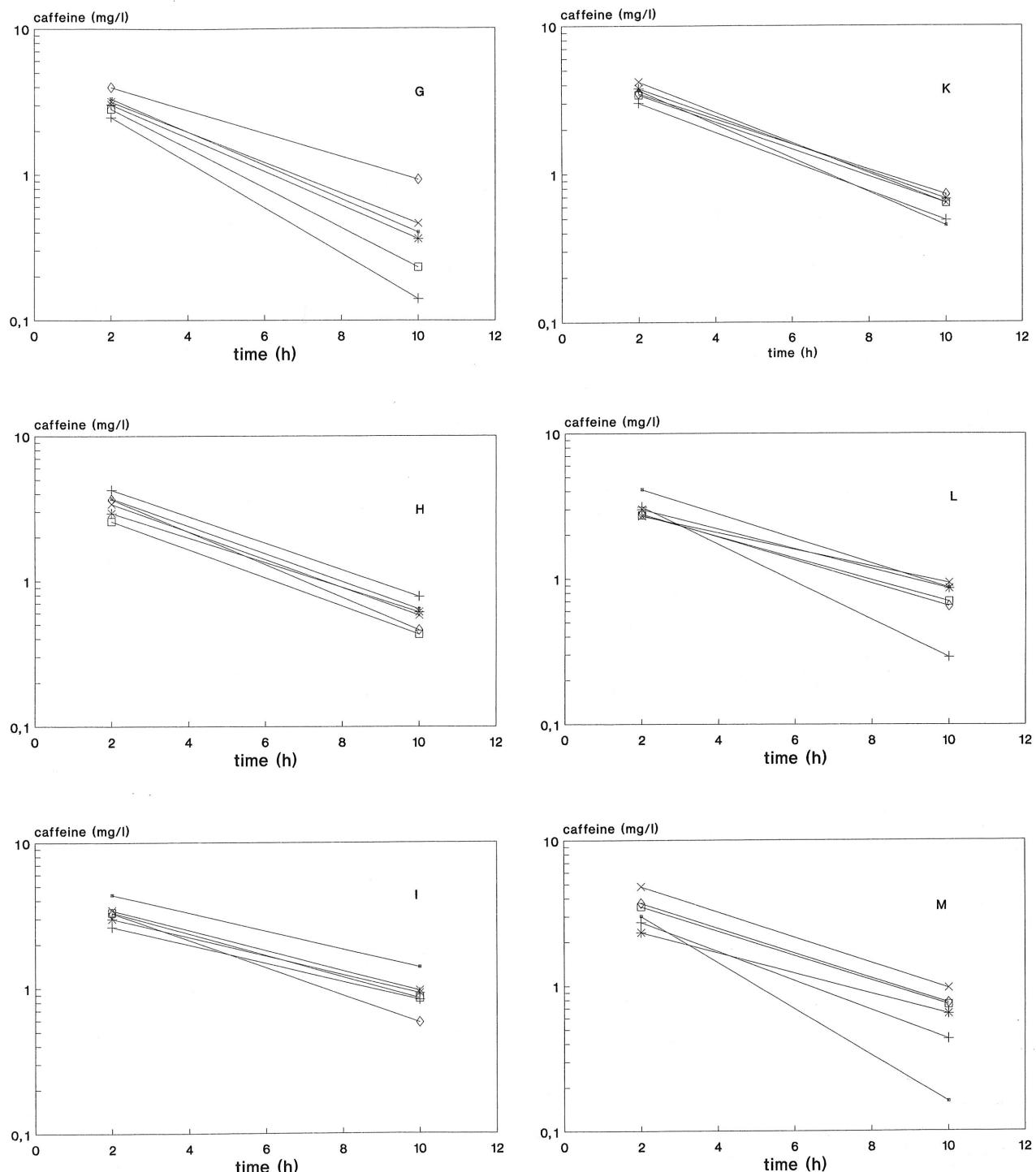


Abb. 1g-m

Fig. 1 Caffeine blood decay curves for each of 12 males who received oral doses on six separate occasions. week 1 □, week 4 +, week 7 *, week 10 □, week 13 x, week 15 Δ

nation of healthy young males appear in Tables 1a and 1b (single values). Both caffeine-clearance and half-life were highly reproducible in each subject on the six occasions on which they were measured, as indicated by the low *intra*-individual CV, which had a mean value of 13.6% for CL_{tot} (range from 1.1 to 26.9%), 17.2% for t_{1/2} (range from 8.7 to 24.5%).

Discussion

Compared to the high reproducibility of caffeine decay curves in each healthy male, caffeine elimination varied more extensively between subjects as reflected by the coefficients of variation of *inter*-individual

Table 1a Caffeine clearance [ml/h/kg] in 12 healthy volunteers

Subject	Weight (kg)	Week 1	Week 4	Week 7	Week 10	Week 13	Week 16	M	X	CV
A	63	196	203	188	223	225	257	206	215	1.2
B	80	63	67	84	105	92	62	76	79	2.2
C	80	127	124	115	95	106	110	113	113	1.1
D	65	136	142	162	113	121	117	129	132	14.4
E	65	242	196	272	212	175	288	227	231	19.0
F	72	245	297	321	363	302	185	300	286	21.7
G	75	178	236	157	106	197	156	168	172	25.4
H	72	147	133	123	146	158	136	141	141	8.7
I	90	93	102	69	114	120	103	103	100	18.0
K	68	177	136	149	156	133	143	146	149	10.8
L	90	89	127	107	123	93	105	106	107	14.3
M	80	118	88	113	158	184	167	138	138	26.9
Median (M)		142	135	136	135	146	140			
Arithmetic mean (X)		151	154	155	160	159	152			
Coefficient of variation (CV)		38.4	42.9	48.4	47.5	39.0	42.8			

$$CV [\%] = \frac{100 \times SD}{\text{arithm. mean}}$$

Table 1b Caffeine half-life [h] in 12 healthy volunteers

Subject	Week 1	Week 4	Week 7	Week 10	Week 13	Week 16	M	X	CV (%)
A	1.9	1.7	2.6	2.2	2.3	2.1	2.2	2.1	16.2
B	5.9	4.9	5.6	3.1	4.6	5.3	5.1	4.9	20.3
C	3.5	4.6	3.6	3.8	2.6	4.2	3.7	3.7	18.3
D	4.2	3.6	3.6	3.9	3.9	3.1	3.8	3.7	10.1
E	2.6	1.8	1.9	3.2	1.9	2.3	2.1	2.2	23.8
F	1.9	1.9	1.3	1.5	1.8	1.9	1.9	1.7	14.9
G	2.6	1.9	2.8	3.8	2.2	2.6	2.6	2.7	24.5
H	2.7	3.2	2.8	3.1	3.5	2.4	3.0	3.0	13.3
I	4.4	4.1	4.9	4.9	3.2	4.7	4.6	4.3	15.9
K	3.1	3.2	3.3	2.7	3.0	3.5	3.2	3.2	8.7
L	3.6	3.8	4.4	4.1	5.0	5.3	4.2	4.4	15.4
M	3.6	3.3	3.5	4.3	1.9	3.0	3.4	3.3	24.4
Median (M)	3.2	3.3	3.4	3.5	2.8	3.1			
Arithmetic mean (X)	3.3	3.4	3.4	3.4	3.0	3.4			
Coefficient of variation (CV)	34.5	33.1	35.6	29.6	34.4	36.43			

Table 2 Intra and inter-individual comparison

		One-sample t-test (pair test)		Two-sample t-test (two independent samples)	
		One-side	Two-side	One-side	Two-side
10%	n =	62	75	121	149
20%	n =	17	22	32	39
30%	n =	9	11	15	19

$\alpha = 0.05$, $1 - \beta = 0.90$, $\sigma = 40$

comparison. These values are similar to the results of other investigators [Balogh 1991, Kalow 1985]. By means of statistical analysis [Fahrmeir and Hamerle 1984], the existence of *inter-individual* variability was proved:

$$H_0: \text{'inter-variability'} = 0$$

This null-hypothesis is rejected, because the test statistics (23.1) is markedly higher than the 0.95-quantil of F-distribution with 11 and 60 degrees of freedom. This means, a variability between subjects can be concluded with a significance level of 5%.

When planning future investigations, the distribution of variance should be considered for the assessment of the sample size. The following decomposition of variances could be assessed from data presented above:

- estimated variance between time points (*intra-individual*) = 960.99 corresponds to 21.4%,
- estimated variance between single volunteers (*inter-individual*) = 3,533.37 corresponds to 78.6%

The knowledge of variance provided precise evidence of the sample size. The number of subjects necessary with acceptance probability of $1 - \beta = 0.90$ to prove previously defined differences of 10, 20 or 30% for both one-side and two-side test and for an *intra-individual*, as well as an *inter-individual* comparison are shown in Table 2.

These results may be a recommendation for all investigators, who use caffeine elimination as a test of biotransformation activity or drug interactions.

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