Eur J Clin Pharmacol (1983) 24: 93–98

European Journal of Clinical Pharmacology

The Absolute Bioavailability of Caffeine in Man

J. Blanchard[1] and S. J. A. Sawers[2]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, USA, and [2]University Department of Therapeutics and Clinical Pharmacology, The Royal Infirmary, Edinburgh, Scotland

Summary. The absolute bioavailability of orally administered caffeine was investigated in 10 healthy adult male volunteers, aged 18.8 to 30.0 years. The subjects were administered a 5 mg/kg dose of caffeine as either an aqueous oral solution or an intravenous infusion, on separate occasions about 1 week apart, in a randomized crossover fashion. Plasma samples were collected over the 24-h period following each dose and assayed for their caffeine content using a high-performance liquid chromatographic technique. The oral absorption was very rapid, reaching a peak (T_p) plasma concentration after 29.8 ± 8.1 min (mean ± SEM). In addition, the variation in the maximum plasma concentration (C_{max}) was low, 10.0 ± 1.0 µg/ml. The absolute bioavailability was assessed by comparing the areas under the plasma concentration vs. time curves for the intravenous and oral doses of caffeine. The rapid absorption resulted in essentially complete bioavailability of the oral caffeine, F(%) = 108.3 ± 3.6%. The caffeine plasma half-lives varied from 2.7 to 9.9 h, indicating substantial inter-subject variability in its elimination.

Key words: caffeine; absolute bioavailability, intra- and inter-subject variability

Caffeine is present in coffee, tea, carbonated beverages, prescription and non-prescription medication, and a variety of foodstuffs, making it one of the most widely-consumed agents in the world. Recently, there has been a renewed interest in the therapeutic potential of caffeine as a result of its success in treating apnea in premature infants (Aranda et al. 1977; Bada et al. 1979). Although some previous studies (Axelrod and Reichenthal 1953; Aranda et al. 1979) have alluded to the "completeness" of caffeine's absorption following oral administration, they were not designed specifically to answer this question and hence did not utilize a suitable study protocol. The present study was therefore initiated in order to investigate more fully the absorption aspects of caffeine's pharmacokinetics and, in particular, to determine the absolute bioavailability of caffeine administered orally in aqueous solution.

Material and Methods

Subject Selection

Ten healthy adult male Caucasian volunteers with a mean age (± SEM) of 21.8 ± 1.1 years were studied. The subjects were assessed as being "healthy" on the basis of a normal health history, physical examination, and electrocardiogram. In addition, the subjects were within normal limits for the following laboratory tests: plasma urea, electrolytes, creatinine, bilirubin, aspartate aminotransferase, alkaline phosphatase, total protein and albumin, creatinine clearance and complete blood count. None of the subjects were taking any prescription or non-prescription medication at the time of the study.

Experimental Protocol

After obtaining informed consent, each subject was administered both an oral and an intravenous dose of caffeine (5 mg/kg), on separate occasions, about 1 week apart using a crossover design. The dosing order was randomized to avoid any confounding effects due to the route of administration employed. All doses were administered at approximately 9:00 a.m. on the day of the kinetic trial. The intrave-

0031-6970/83/0024/0093/$01.20

nous dose of caffeine was prepared by diluting the appropriate quantity of the injectable caffeine preparation (Caffeine and Sodium Benzoate Injection, USP, Eli Lilly and Company, Indianapolis, IN 46206, USA) with isotonic sodium chloride solution (Sodium Chloride Injection, B.P., Travenol Laboratories, Thetford, Norfolk, UK) to produce 50 ml of infusion solution. The infusion solution (30 ml) was then administered via a heparin lock placed in a forearm vein at a constant rate of 1 ml/min using a previously calibrated infusion pump (Braun Unita 1, Braun, Melsungen AG, FRG). The oral dose consisted of 200 ml of an aqueous caffeine (Caffeine, Baker Grade, J.T. Baker Chemical Co., Phillipsburg, NJ 08865, USA) solution which was ingested rapidly. The glass containing the oral dose and the subject's oral cavity were then rinsed with 2 additional 50 ml portions of distilled water to ensure that the entire dose was consumed. The complete oral dosing procedure was accomplished in less than a minute with zero time being considered the mid-point of this interval. Each subject was fasted from the previous evening until at least 2 h after the administration of the oral dose. However, they were allowed a light breakfast the morning of the intravenous dose. Subjects were instructed to abstain from caffeine-containing foods and beverages, tobacco (9 of the 10 subjects were non-smokers) and alcohol from 72 h before, until 24 h after each administration of caffeine. The absence of caffeine in each subject's plasma was confirmed by assaying a blood sample collected immediately before each dose was administered (i.e., at time zero).

Five ml blood samples were withdrawn via a heparin lock placed in an arm vein (contralaterally in the case of the intravenous dose) at time zero and at the following times after the start of the infusion: 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 150, 210, 270, 390, 570, 750, 930 and 1,470 min. Since the oral dose was administered as a bolus, the sampling times were 0, 15, 30, 45, 60, 120, 180, 240, 360, 540, 720, 900 and 1,440 min post-dosing. Prior to the removal of each 5 ml blood sample, 2 ml of blood was withdrawn through the heparin lock and discarded. The 5 ml blood samples were then collected in a new syringe and transferred immediately to heparinized tubes. In each case, the last 3 samples were collected using individual venipuncture. Measurements of pulse rate and blood pressure were made at each sampling time. For the first 3 h following intravenous dosing, the electrocardiograph of each subject was monitored continuously with an Oxford Medilog recording system (Oxford Medical Systems Ltd., Abingdon, Oxford, UK) using a modified lead V_5 chest electrode. Each recording was later analyzed using a Pathfinder II (Reynolds Medical Ltd., Hertford, UK) high speed electrocardiograph analyzer. Blood samples were centrifuged immediately after collection and the plasma stored in tightly-sealed glass tubes at −20 °C until assayed. The procedure used for assaying plasma samples was essentially as described previously (Blanchard et al. 1980; Blanchard et al. 1981), except that the plasma was deproteinized with an equal volume of 12% w/w perchloric acid. The intravenous and oral solutions administered to the subjects were also assayed in this manner in order to establish the actual doses used.

Data Treatment

The plasma caffeine concentration vs. time data were fitted to both a one- and a two-compartment open model on a Burroughs Model 6900 digital computer using a nonlinear optimization technique based on the simplex algorithm of Nelder and Mead (1965) and the weighting factor recommended by Ottaway (1973). The most appropriate compartmental model for each data set was determined using the criteria of Boxenbaum et al. (1974) and the "law of parsimony" described by Riggs (1963). Samples with caffeine concentrations less than 0.5 μg/ml were not included in the data analysis since this concentration was determined to be the minimum required for accurate quantitation.

Areas under the plasma concentration-time curves extrapolated to infinity (AUC_0^∞) were calculated from the computer generated function of best fit. The "absolute" bioavailability (F) of the oral caffeine doses was calculated using either Equ. (1) or (2),

$$F = \left[\frac{AUC_0^\infty}{D}\right]_{oral} \Big/ \left[\frac{AUC_0^\infty}{D}\right]_{iv} \quad (1)$$

$$F = \left[\frac{(AUC_0^\infty)k}{D}\right]_{oral} \Big/ \left[\frac{(AUC_0^\infty)k}{D}\right]_{i.v.} \quad (2)$$

where: D = the dose [mg/kg], k = the apparent first-order elimination rate constant [min^{-1}] for data exhibiting one-compartment characteristics, (AUC_0^∞) = the area under the plasma concentration vs. time curve from time zero to infinity [$\mu g \cdot min \cdot ml^{-1}$], and the subscripts "oral" and "i.v." refer to the route of administration studied. For data exhibiting two-compartment kinetics, the value of k in Equs. (1) and (2) was replaced by β, the rate constant for the terminal log-linear disposition phase, which is determined from the slope of the terminal linear segment of a semi-logarithmic plot of plasma concentration vs. time and from which the β phase half-life is determined as:

Table 1. Oral absorption characteristics of caffeine in 10 young men

Parameter	Value of Parameter		
	Mean	SEM	Range
Age [years]	21.8	1.1	18.8–30.0
Weight [kg]	79.5	3.9	64–106
Oral Dose			
[mg]	393.3	20.2	315.0–530.0
[mg/kg]	4.94	0.03	4.84–5.17
i.v. Dose	NS	NS[b]	
[mg]	385.5	20.7	300.2–503.7
mg/kg	4.85	0.09	4.64–5.63
β [min^{-1}][a]			
Oral	NS 0.00258	0.00029	0.00126–0.00426
i.v.	0.00228	0.00026	0.00117–0.00388
AUC_0^∞ ($\mu g \cdot min \cdot ml^{-1}$)			
Oral	4142.5	549.1	1933.4–7345.7
	NS (4188.2)[d]	(554.9)[d]	(1949.9–7424.9)[d]
i.v.	4143.3	615.1	2174.0–8372.8
	(4213.8)[d]	(547.1)[d]	(2341.9–7440.5)[d]
Bioavailability Parameters			
F [%]	108.3	3.6	93.8–129.7
Tp [min][c]	29.8	8.1	3.6–79.8
C_{max} [$\mu g/ml$]	9.9	1.1	6.9–16.1
	(10.0)	(1.0)	(6.9–16.2)

[a] β for two-compartment data or k for one-compartment data
[b] Differences not significant
[c] Corrected for the absorption lag time
[d] Values in parentheses have been normalized to a dose of exactly 5 mg/kg in each subject

$$t_{½(\beta)} = \frac{\ln 2}{\beta} \tag{3}$$

The conditions under which Equs. (1) and (2) are valid for two-compartment data were recently discussed by Chiou et al. (1981).

The use of Equ. 1 to calculate F is based upon the assumption that the clearance of the drug remains constant between treatments whereas equation 2 is based upon the assumption that the volume of distribution is constant between treatments and that the variation in clearance can be accounted for by β (k) alone. The choice between Equs. (1) and (2) for calculating a given subject's F value was based upon the statistical considerations discussed by Upton et al. (1980). In the case of oral doses exhibiting one-compartment characteristics, the time at which the peak caffeine plasma concentration was achieved (Tp) and the value of the maximum (peak) caffeine concentration (C_{max}) were calculated from Equs. (4) and (5):

$$Tp = \frac{\ln (ka/k)}{(ka-k)} + t_L \tag{4}$$

$$C_{max} = \frac{FD}{V_d} e^{-kT_p}, \tag{5}$$

where, ka = the apparent first-order absorption rate constant [min^{-1}], F = the fraction of the dose absorbed, t_L = the absorption lag time, and V_d = the apparent volume of distribution, calculated as:

$$V_d = \frac{\text{Dose}}{k \cdot (AUC_0^\infty)} \tag{6}$$

For data exhibiting two-compartment characteristics, the volume of distribution during the post-distributive phase (V_{d_β}) was calculated from Equ. (6) with k replaced by β. For subjects exhibiting two-compartment characteristics following oral dosing Tp and C_{max} were obtained by substituting various values of time into the "best-fit" equation until the maximum value of C was obtained.

Statistical Analysis

The various parameters related to the oral and intravenous doses were compared using the two-tailed Student's *t* test for paired data with $p < 0.05$ taken as the minimum level of significance.

Results

The randomization procedure resulted in 5 subjects receiving the oral dose first and 5 subjects receiving the intravenous dose first, thereby minimizing any potential influence of the treatment (dosing) sequence. None of the subjects exhibited any arrhythmias following the oral or intravenous doses of caffeine. Two subjects noted some light-headedness after the oral dose which occurred at about the time at which their peak levels (C_{max}) were attained. One subject noted some light-headedness at the end of his intravenous infusion, which would also correspond closely with his peak level. No other side effects were experienced.

The absorption characteristics of orally administered caffeine are summarized in Table 1. These data illustrate several points. Firstly, there were no statistically significant differences between the doses given by the two routes of administration. This is an important consideration since there is a potential for altered pharmacokinetics when substantially different doses are compared, which could confound the interpretation of the data. In addition, there was no statistically significant difference between the mean β (k) values due to the route of administration, in spite of fairly large changes in some interindividual β (k) values. An example of this effect is illustrated by the data for subject (J.S.) shown in Fig. 1.

In this subject and one other, the "β correction" [i.e., the use of Equ. (2) instead of Equ. (1)] to a large degree accounted for these differences and resulted in F values in these subjects of 103.0% and 109.2%, as opposed to 69.0% and 56.1%, respectively if no β correction were applied, indicating that their volumes of distribution were approximately constant

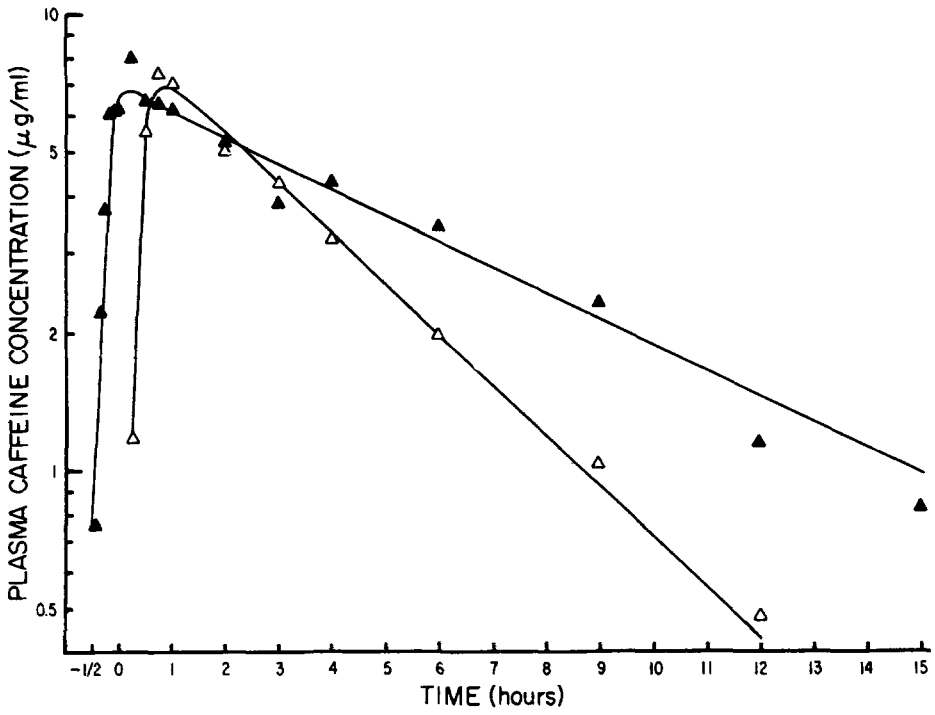

Fig. 1. Plasma caffeine concentration vs. time data in subject JS following intravenous (▲——▲) and oral (△——△) doses of 4.76 and 4.96 mg/kg, respectively. The oral dose was given 18 days after the intravenous dose. The half-life in this subject is 162.7 min following the oral dose and 316.5 min following the intravenous dose

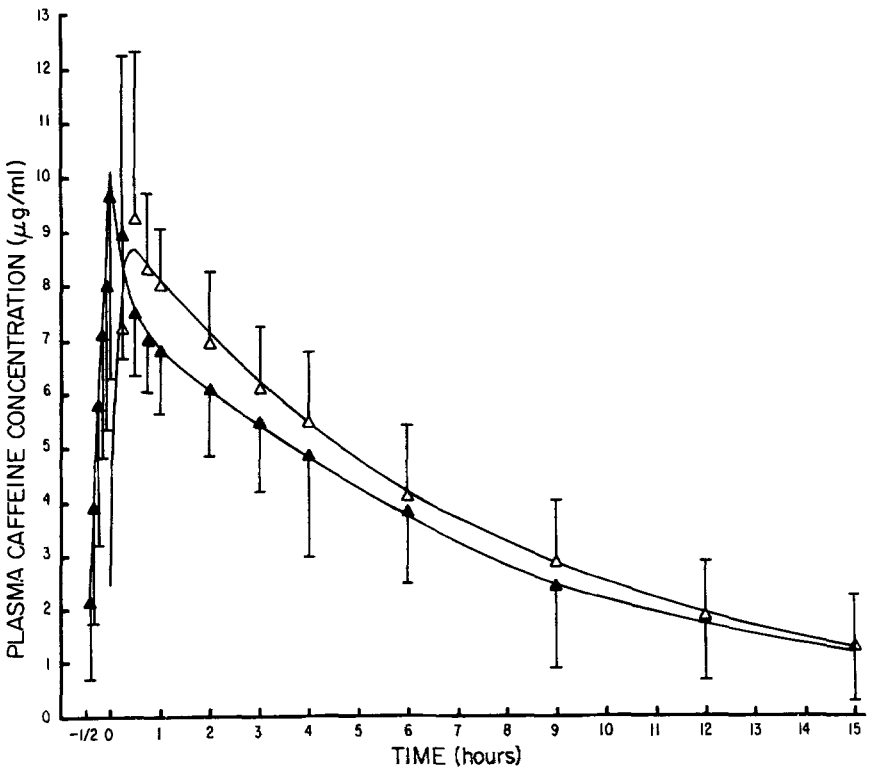

Fig. 2. Mean plasma caffeine concentrations in young men ($n = 10$) following intravenous (▲——▲) and oral (△——△) doses of 5 mg/kg. Vertical bars represent one standard deviation

between treatments (Upton et al. 1980). It should be noted that the half-lives following oral dosing were substantially shorter than those following intravenous dosing in both of these individuals so that the intra-subject differences in half-life were not due a prolonged absorption of the drug, a condition which could invalidate the use of the β correction (Koup and Gibaldi 1980). In another two subjects both the volumes of distribution and the β values apparently changed substantially between treatments and, therefore, the application of the β correction was not appropriate.

The use of the β correction here produced F values of 146.6% and 140.8% which were artifically high in comparison to the "uncorrected" F values of 129.7% and 121.9%, respectively. These examples illustrate how the application of the β correction can be valuable in some instances and counterproductive at other times as noted earlier by Upton et al. (1980).

The dose-normalized areas under the plasma concentration vs. time curve from time zero to infinity (AUC_0^∞) were not significantly different. The percentage of the caffeine dose absorbed, F (%), following its administration orally as an aqueous solution ranged from 93.8 to 129.7% with a mean ± SEM of 108.3 ± 3.6%. In addition, the plasma concentration peaked quite rapidly (i.e., 29.8 ± 8.1 min), producing a mean maximum concentration of 9.9 ± 1.1 μg/ml. The essentially complete bioavailability of the caffeine following oral dosing is illustrated by the close similarity of the "average" oral and intravenous curves shown in Fig. 2.

Discussion

The present study illustrates that the gastrointestinal absorption of caffeine from an aqueous solution is very rapid and essentially 100% complete when administered to young, healthy, fasted male volunteers. The results also indicate that no significant first-pass effect occurs following the oral administration of caffeine at doses of 5 mg/kg, in contrast to results from animal studies wherein first-pass effects were observed (Aldridge et al. 1977). Data from two subjects following oral dosing and five subjects following intravenous dosing were best described by a two-compartment open model. The remaining data were described adequately by a one-compartment open model. The route of administration did not appear to affect the elimination of the drug substantially since the mean β (k) values were not significantly different following the oral and intravenous doses, as shown in Table 1. However, as noted previously, the β (k) value changed substantially between treatments in 2 of the 10 subjects. Such intra-individual variability in elimination has recently been reported for the related methylxanthine theophylline as well as other drugs (Rowland 1980).

The subjects studied here were all healthy and medication-free and had been instructed to abstain from caffeine-containing foods and beverages, tobacco and alcohol from 3 days before until 24 h after each dose of caffeine. In addition, the oral and intravenous doses were given quite close together in time, with the mean period between doses being 7.4 ± 4.4 days; range = 4 to 18 days, exclusive of one subject (J.T.) whose i.v. dose was given 42 days after his oral dose. Thus there is no apparent reason for the dramatic changes in either the volumes of distribution or the β (k) values observed in some of the subjects. Since caffeine undergoes extensive metabolism in the liver it is possible that changes in certain environmental influences such as exposure to cigarette smoke, organic chemicals, or nutritional factors, etc. may have occurred between the oral and intravenous doses to account for the changes in β (k) and/or the volume of distribution. Other possible sources of inter- and intra-subject variability and their relationship to bioavailability studies have been discussed in detail by Tozer (1979).

The mean half-lives (calculated as the harmonic mean) were comparable following oral (4.5 h) and intravenous (4.1 h) dosing, with individual values ranging from 2.7 to 9.9 h. The broad range of half-lives indicates that, in addition to the intra-subject variability noted above, there is also a substantial inter-subject variability in the elimination rate of caffeine.

Acknowledgements. We thank the members of the technical staff of the Dept. of Therapeutics and Clinical Pharmacology, The Royal Infirmary, Edinburgh, Scotland, for their assistance with several aspects of this study. One of us (J. B.) is particularly grateful to Dr. L. F. Prescott for hosting his sabbatical leave and to the J. E. Fogarty International Center and the National Institute on Aging, Bethesda, Maryland, for the receipt of a fellowship number 1 FO6 TW00491-01. Sincere thanks are also extended to Dr. J. A. Clements for the use of his digital computer program and his helpful comments.

These studies were performed at the Edinburgh Royal Infirmary.

References

1. Aldridge A, Parsons WD, Neims AH (1977) Stimulation of caffeine metabolism in the rat by 3-methylcholanthrene. Life Sci 21: 967–974
2. Aranda JV, Cook CE, Gorman W, Collinge JM, Loughnan PM, Outerbridge EW, Aldridge A, Neims AH (1979) Pharmacokinetic profile of caffeine in the premature newborn infant with apnea. J Pediatr 94: 663–668
3. Aranda JV, Gorman W, Bergsteinsson H, Gunn T (1977) Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. J Pediatr 90: 467–472
4. Axelrod J, Reichenthal J (1953) The fate of caffeine in man and a method for its estimation in biological material. J Pharmacol Exp Ther 107: 519–523
5. Bada HS, Khanna NN, Somani SM, Tin AA (1979) Interconversion of theophylline and caffeine in newborn infants. J Pediatr 94: 993–995

6. Blanchard J, Mohammadi JD, Conrad KA (1980) Improved liquid-chromatographic determination of caffeine in plasma. Clin Chem 26: 1351–1354
7. Blanchard J, Mohammadi JD, Trang JM (1981) Elimination of a potential interference in assay for plasma caffeine. Clin Chem 27: 637–639
8. Boxenbaum HG, Riegelman S, Elashoff RM (1974) Statistical estimations in pharmacokinetics. J Pharmacokin Biopharm 2: 123–148
9. Chiou WL, Lui CY, Lam G (1981) Plasma area method in relative bioavailability evaluation of drugs with changing biological half-lives. J Pharm Sci 70: 109–112
10. Koup JR, Gibaldi M (1980) Some comments on the evaluation of bioavailability data. Drug Intell Clin Pharm 14: 327–330
11. Nelder JA, Mead R (1965) A simplex method for function minimization. Comput J 7: 308–313
12. Ottaway JH (1973) Normalization in the fitting of data by iterative methods. Biochem J 134: 729–736
13. Riggs DS (1963) The mathematical approach to physiological problems. Williams and Wilkins, Baltimore, MD, p 51
14. Rowland M (1980) Intra-individual variability in pharmacokinetics. In: Breimer DD (ed) Towards better safety of drugs and pharmaceutical products. Elsevier/North-Holland Biomedical Press, New York, pp 143–151
15. Tozer TN (1979) Pharmacokinetic principles relevant to bioavailability studies. In: Blanchard J, Sawchuk RJ, Brodie BB (eds) Principles and perspectives in drug bioavailability. Karger, Basel, pp 120–155
16. Upton RA, Riegelman S, Sheiner LB (1980) Bioavailability assessment as influenced by changes in drug disposition. In: Albert KS (ed) Drug absorption and disposition: statistical considerations. Am Pharm Assoc, Washington, DC, pp 77–86

Received: April 14, 1982
accepted in revised form: July 2, 1982

Dr. J. Blanchard
College of Pharmacy
University of Arizona
Tucson, Arizona 85721, USA