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Comparative Pharmacokinetics of Caffeine in Young and Elderly Men

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The pharmacokinetic behavior of caffeine was compared in a group of eight healthy young men aged 20.5 ± 2.0 years (mean ± SD), and in a group of eight healthy, elderly men aged 71.2 ± 3.9 years. Each subject was given a 5 mg/kg dose of caffeine as either an aqueous oral solution or an intravenous infusion over 30 min using a randomized crossover design. Plasma and urine samples were collected for 24 hr following each dose and analyzed for caffeine content using high-performance liquid chromatography.

The peak times (t_{max}), peak concentrations (C_{max}), and the percentage of the peroral dose systemically available, F(%), were essentially identical in both age groups, indicating that caffeine was absorbed rapidly and completely after peroral administration. These results also indicated that the first-pass metabolism observed in rats following the peroral administration of caffeine does not occur in either human group studied here. The elimination of caffeine during its terminal disposition phase was log-linear. Several between-group comparisons of other pharmacokinetic parameters were made. Although the average elimination rate constant was greater in the elderly, the difference did not reach statistical significance, possibly because of the considerable intersubject variability in the elimination rate of caffeine, with half-lives ranging from 2.27 to 9.87 hr. The average apparent volume of distribution was significantly lower in the elderly subjects while the clearances were slightly, but not significantly, larger in the elderly subjects. It appears that most aspects of the pharmacokinetic behavior of caffeine are very similar in young and elderly men.

KEY WORDS: caffeine; pharmacokinetics; comparative, young, elderly, men.

INTRODUCTION

Caffeine, ethanol, and nicotine share unique acclaim as the three most widely consumed psychoactive agents in the world (1). Caffeine and two related alkaloids, theophylline and theobromine, occur in plants widely distributed throughout the world. More than a billion kilograms of coffee

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are consumed annually in the United States alone (2). Tea consumption is only 25% that of coffee in America, but this constitutes more than forty billion servings per year (1). In addition, caffeine is present in cocoa and many carbonated beverages as well as a variety of over-the-counter and prescription medications. It has been established that the average coffee drinker consumes approximately 300 mg of caffeine per day with 20 to 30% of adult Americans consuming up to 600 mg of caffeine per day and 10% possibly consuming more than 1000 mg per day (1).

In the past decade, several authors have discussed the physiologic changes accompanying aging and the resulting alterations in pharmacokinetic characteristics observed in the elderly (3–7). Although the pharmacokinetics of caffeine have been studied in young subjects (8–11), and recently in elderly subjects (12), no studies have yet appeared specifically addressing the question of the effect of age on the pharmacokinetics of this widely consumed agent. The goal of this study was to compare the pharmacokinetic behavior of caffeine in a group of healthy, active young men and in a group of healthy, active elderly men, utilizing both intravenous and peroral dosing, with a view toward comparing the absorption, as well as distribution and elimination, in these two groups.

MATERIALS AND METHODS

Subjects

Two groups of subjects were studied. Group 1 consisted of eight young Caucasian males aged 18.8 to 24 years (mean = 20.5 years). Group 2 consisted of eight elderly Caucasian males aged 66 to 78.2 years (mean = 71.2 years). The elderly group were recruited from local social clubs while the young group were either soldiers or university students. All subjects led active, normal lives; no hospitalized patients were used. Each subject gave written informed consent to participate in the study, which was approved by the Ethics Advisory Committee of the Edinburgh Royal Infirmary.

None of the subjects showed any evidence, on history or examination, of cardiac, renal, hepatic, gastrointestinal, or other disease. In addition, the following laboratory parameters were normal: plasma; urea, electrolytes, creatinine, bilirubin, aspartate aminotransferase, alkaline phosphatase, total protein and albumin, creatinine clearance, complete blood count, and electrocardiogram.

None of the subjects were taking any medications. One of the young and one of the elderly group were light cigarette smokers (less than 10 cigarettes per day) while two of the elderly group were pipe smokers. The

remaining subjects were nonsmokers. Two of the young and two of the elderly subjects were nondrinkers while the remainder admitted modest consumption of alcohol. One of the young group drank less than three cups of tea or coffee per day, and one of the elderly group drank up to eight cups per day. The remaining subjects normally consumed three to six cups daily.

Methods

Each subject was studied twice; once after peroral caffeine and once after intravenous caffeine. The order of administration was randomized by tossing a coin, and the two experiments were separated by a minimum of three days, and usually by about one week. The subjects were asked to abstain from tea, coffee, or other caffeine-containing beverages, caffeine-containing foods, alcohol, and smoking for three days prior to and for the duration of each experiment. In order to help ensure compliance in those subjects who found it difficult to abstain from coffee and tea during the experimental period, each subject was provided with an 8 oz. tin of either Barleycup® or Caro®, two commercially available hot-drink mixes consisting of roasted cereal grains and chicory, but no caffeine. Compliance with the caffeine-free regimen was verified by assaying "blank" specimens of plasma and urine collected immediately before each dose was administered, i.e., at time zero.

The subjects were fasted from 10:00 p.m. the night before until at least 2 hr after the peroral administration of caffeine, but were allowed to take a normal breakfast on the morning of the intravenous experiment. Each subject received their peroral or intravenous dose of caffeine (5 mg/kg) at 9:00 a.m., following which blood and total urine samples were collected for 24 hr. The intravenous dose of caffeine (caffeine and sodium benzoate injection, U.S.P., Eli Lilly and Co., Indianapolis, IN 46206) was diluted with sufficient isotonic saline (sodium chloride solution, B.P., Travenol Laboratories, Ltd., Thetford, Norfolk, England) to produce 50 ml of infusion fluid, 30 ml of which was administered into an arm vein via an indwelling heparinized cannula (Venflon, Viggo 18G, Viggo AB, Helsingborg, Sweden) at a constant rate of 1 ml/min using a previously calibrated infusion pump (Braun Unita 1, Braun, Melsungen AG, West Germany). The peroral dose consisted of caffeine (caffeine, Baker grade, J. T. Baker Chemical Co., Phillipsburg, NJ 08865) dissolved in 200 ml of distilled water, which was ingested rapidly, following which the container and the subject's mouth were rinsed with two 50 ml portions of distilled water to ensure that the entire dose was administered. This procedure took 1 min or less to complete and zero time was recorded as the midpoint of the dosing interval.

Blood samples (5 ml) were collected via an indwelling heparinized cannula which, in the case of the intravenous experiment, was sited in the arm opposite to the one used for the infusion. The blood sampling times following the start of the intravenous infusion were: 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 150, 210, 270, 390, 570, 750, 930, and 1,470 min. Sampling times following peroral dosing were: 15, 30, 45, 60, 120, 180, 240, 360, 540, 720, 900, and 1,440 min. Prior to the collection of each blood sample via the indwelling cannula, 2 ml of blood was withdrawn and discarded using a separate collection syringe. The 5 ml blood samples were then collected in a new syringe and transferred immediately to heparinized tubes. The last three blood samples were collected by individual venipuncture. All samples were centrifuged within 1 hr after collection and the plasma harvested and stored at −20°C until assayed for caffeine content. During the course of this study the stability of caffeine in plasma samples stored at −20°C was investigated using high-performance liquid chromatographic analysis. It was found that the caffeine remained stable over the $4\frac{1}{2}$ month period examined. The total volume of the 24-hr urine sample was measured and two 20 ml aliquots were retained. One aliquot of urine, together with an additional 5 ml aliquot of the 24-hr plasma, was assayed for creatinine as part of the creatinine clearance determination; the other aliquot of urine was stored at −20°C for subsequent caffeine assay.

For the first 3 hr following intravenous dosing, each subject's electrocardiograph was monitored continuously with an Oxford Medilog recording system (Oxford Medical Systems Ltd., Abingdon, Oxon, England) using a modified lead V_5 chest electrode. Each recording was later analyzed using a Pathfinder II high speed electrocardiograph analyzer (Reynolds Medical Ltd., Hertford, England). Measurements of pulse and blood pressure were made at each sampling time. Due to the above monitoring procedures, the subjects were asked to lie or sit up in bed for the first 3 hr following the intravenous dose, whereas they were allowed to sit on a chair or walk about the room following the peroral dose.

Analytical Procedures

Caffeine analyses in plasma and urine were performed using the procedures described previously (13,14) except that the precipitation of plasma proteins was performed using an equal volume of 12% w/w perchloric acid. All intravenous and peroral doses administered to the subjects were assayed using this procedure. Urine assays were performed in the identical manner described previously (14). Urine creatinine concentrations were determined on a Beckman Analyzer employing the Jaffé reaction (15) while plasma creatinine was determined using a Sigma kit (Sigma Chemical Co., St. Louis, MO 63178), which also utilized the Jaffé reaction.

In order to compare more fully the effect of age on the metabolic capacity of the liver, both the clearances and the apparent volumes of distribution of the unbound drug were determined by dividing the calculated clearances and volumes of distribution for total drug in each subject by the unbound fraction of drug measured in that subject (16).

Data Analysis

Caffeine plasma concentration versus time data were fitted to both a one- and a two-compartment open pharmacokinetic model using nonlinear least-squares regression employing a simplex optimization procedure (17) and the weighting factor recommended by Ottaway (18). Samples containing less than 0.5 μg/ml were not included in the data analysis since this concentration was previously determined to be the minimum required for accurate quantitation. The most appropriate model for a given data set was determined employing the criteria proposed by Boxenbaum *et al.* (19) and the "law of parsimony" described by Riggs (20). The areas under the plasma concentration versus time curves from time zero to infinity (AUC) were calculated from the computer generated function of best fit. The remaining pharmacokinetic parameters were then calculated using well-known methods (21).

Since the computer program utilized fit the intravenous data to an equation (see Eq. 244 of ref. 21) describing the time course of the caffeine both during the infusion and after its cessation, the intercepts of the line of best fit were automatically corrected to zero time. The peroral data were fitted to both Eq. (1) (one-compartment) and Eq. (2) (two-compartment) to determine the most applicable model:

$$C = C(0)(e^{-\lambda_z(t-t_{lag})} - e^{-K_{01}(t-t_{lag})}) \tag{1}$$

$$C = C_1 e^{-\lambda_1(t-t_{lag})} + C_z e^{-\lambda_z(t-t_{lag})} - (C_1 + C_z) e^{-K_{01}(t-t_{lag})} \tag{2}$$

In 7 of the 32 kinetic studies, the "blank" samples contained small but measurable amounts of caffeine. In these cases, the AUC was corrected by subtracting from it the area contributed by the blank caffeine concentration (C_{blank}) as follows:

$$AUC_{corrected} = AUC_{measured} - \frac{C_{blank}}{\lambda_z} \tag{3}$$

The renal clearance CL_R of caffeine was calculated using a one-point determination as follows:

$$CL_R = \frac{Ae(0-24)}{AUC(0-24)} \tag{4}$$

where $Ae(0-24)$ is the amount of caffeine excreted in the 24 hr post dosing,

and $AUC(0-24)$ is the area under the plasma concentration versus time curve from 0 to 24 hr. The metabolic (nonrenal) clearance (Cl_{NR}) was then calculated as the difference between the total plasma drug clearance (CL) and CL_R:

$$CL_{NR} = CL - CL_R \tag{5}$$

The fraction of the peroral dose systemically available (F) was calculated using either Eq. (6) or (7) shown below:

$$F = \frac{AUC_{po} \cdot D_{iv}}{AUC_{iv} \cdot D_{po}} \tag{6}$$

$$F = \frac{AUC_{po} \cdot D_{iv} \cdot \lambda_{zpo}}{AUC_{iv} \cdot D_{po} \cdot \lambda_{ziv}} \tag{7}$$

where: λ_z is the elimination rate constant of the terminal log-linear disposition phase, D is the dose, and the subscripts *po* and *iv* refer to the route of administration studied. The selection of which of these two equations to use in calculating the F value for a given subject was based upon the statistical considerations discussed by Upton *et al.* (22).

The total body clearance of drug from plasma (CL) and the volume of distribution (V) during the terminal (λ_z) phase after distribution equilibrium has been achieved were calculated as follows:

$$CL = \frac{D_{iv}}{AUC} \tag{8}$$

and

$$V = \frac{CL}{\lambda_z} \tag{9}$$

For subject data exhibiting one-compartment characteristics following peroral dosing, the time to reach the maximum or peak plasma concentration following drug administration (t_{max}) and the value of the maximum concentration (C_{max}) were calculated from Eqs. (10) and (11):

$$t_{max} = \frac{\ln (K_{01}/k)}{(K_{01} - k)} + t_{lag} \tag{10}$$

$$C_{max} = \frac{FD}{V} e^{-kt_{max}} \tag{11}$$

where K_{01} is the first-order absorption rate constant (min^{-1}), k is the first-order elimination rate constant (min^{-1}), t_{lag} is the absorption lag time, and V_1 is the volume of the central or plasma compartment, calculated

from Eq. (9) after replacing λ_z with k (i.e., in the one-compartment model, $V = V_1$ and $\lambda_z = k$). For subjects whose data exhibited two-compartment characteristics following peroral dosing, t_{max} and C_{max} were obtained by substituting various values of time (t) into the "best-fit" equation until the maximum value of C was obtained. Differences in pharmacokinetic parameters between the young and elderly groups were assessed using a two-tailed Student's t test for unpaired data, while differences due to route of administration within a subject group were assessed using the same test for paired data. In each case, $p < 0.05$ was taken as the minimum level of significance.

RESULTS

No arrhythmias were recorded in any of the young subjects after either peroral or intravenous caffeine. In six of the elderly group, sporadic ventricular extrasystoles were noted in the basal recording, but these did not increase in frequency following either peroral or intravenous caffeine. Two of the young subjects experienced some light-headedness about 10 min after the peroral dose, but not during the intravenous infusion. One young subject experienced a similar sensation around the end of the infusion, but not after the peroral dose. No other side effects were recorded.

The mean plasma concentration versus time data following single peroral and intravenous doses in young and elderly subjects are shown in Figs. 1 and 2, respectively. The continuous lines drawn through the data points represent the curves of best-fit calculated using the mean plasma concentrations at each time point. The intravenous data shown in Fig. 2 represent a one-compartment model. Although the data fitted a two-compartment model much better in terms of both the visual appearance and the weighted sum of squares, the difference was not great enough to achieve statistical significance using a $p < 0.05$ criterion and the F test described by Boxenbaum *et al.* (19). Thus the law of parsimony was invoked and the one-compartment fit reported.

Table I illustrates some of the demographic and laboratory parameters measured in the two groups studied. These data, together with the other laboratory findings, physical examinations, and health histories, demonstrate that the subjects were all in good health and apparently free of any disease that could confound the interpretation of results. In addition, the use of male subjects only ensured that there would be no sex-linked variations in the pharmacokinetics of caffeine.

Table II summarizes the comparative absorption characteristics of caffeine in young and elderly men. These data illustrate how the peroral

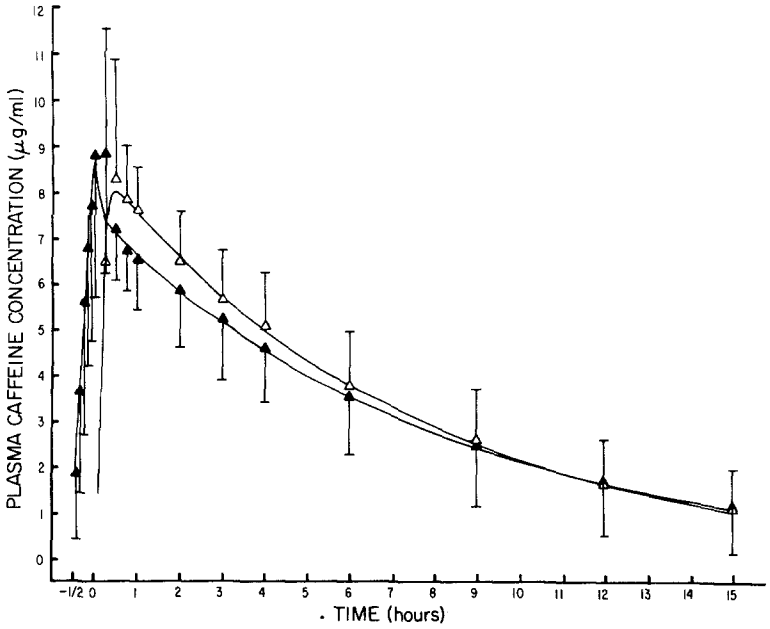

Fig. 1. Mean plasma caffeine concentration vs. time profiles in young men ($N = 8$) following peroral (△—△) and intravenous (▲—▲) doses of 5 mg/kg. The vertical bars represent one standard deviation.

and intravenous doses given to the subjects were essentially identical within each group as well as between each group, and very close to the desired dose of 5 mg/kg. This is a prerequisite for this type of comparison since there is a potential for altered drug kinetics when substantially different doses are given, which could confound the data interpretation. The results also indicate that caffeine was absorbed rapidly in both groups, reaching a peak at about 33–38 min and attaining an average peak concentration of about 9 μg/ml in each group. The absorption rate constants and the absorption lag times were not significantly different between the two groups. The mean half-lives of the absorption process, calculated as ln 2/the mean K_{01}, were 2.05 and 5.73 min in the young and elderly groups, respectively. The absorption lag times varied from less than a minute to nearly 13 min and averaged about 8.8 min in the young group and 5.5 min in the elderly group. Again, these differences were not statistically significant. Thus, while the young subjects were slower in starting to absorb caffeine, their somewhat shorter absorption half-lives resulted in them achieving a peak concentration (C_{max}) at essentially the same time as the elderly group. While the estimates of K_{01} and t_{lag} shown in Table II indicate that the absorption

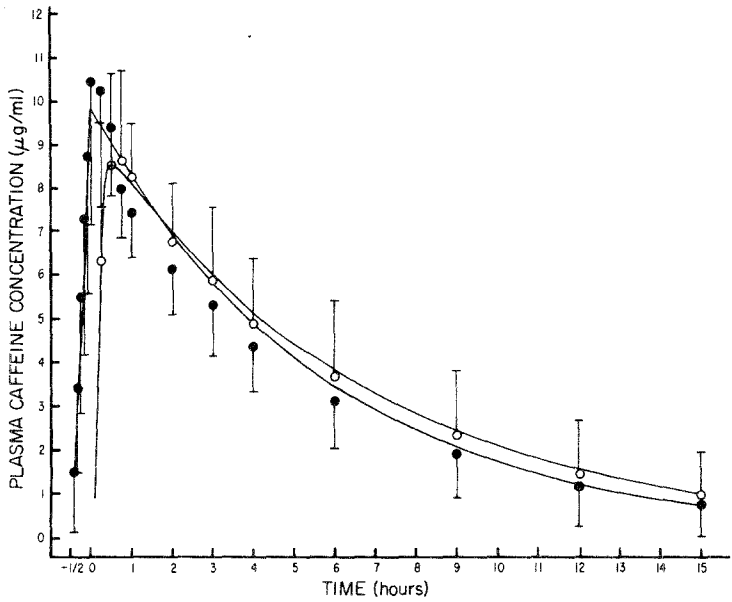

Fig. 2. Mean plasma caffeine concentration vs. time profiles in elderly men ($N=8$) following peroral (○—○) and intravenous (●—●) doses of 5 mg/kg. The vertical bars represent one standard deviation.

Table I. Selected Demographic and Laboratory Findings in Subjects at the Time of Their Kinetic Trials

Parameter	Young group ($N=8$)		Elderly group ($N=8$)		Probability (young vs. elderly)
	Mean	SD	Mean	SD	
Age (yr)[a]	20.45	2.01	71.20	3.94	$p<0.001$
Height (cm)	178.00	3.69	166.63	4.96	$p<0.001$
Weight (kg)	74.36	5.81	70.15	8.85	NS[d]
Percent of average weight[b]	104.53	6.53	99.37	14.61	NS
Body surface area (m^2)	1.92	0.08	1.78	0.09	$p<0.01$
Creatinine clearance (ml/min/1.73 m^2)[c]	93.81	15.57	67.82	13.79	$p<0.005$

[a] Calculated from birth to the median day between the peroral and intravenous trials.
[b] Calculated employing tabular data found in ref. 23. For the elderly group, the age 60–69 values were used as no values could be found for men over 69 years of age.
[c] Values for each subject were calculated as the means from two urine samples (peroral and intravenous), each measured twice by independent methods.
[d] Differences not significant.

Table II. Comparative Absorption Characteristics of Caffeine in Young and Elderly Men

Parameter	Young group ($N = 8$) Mean	SD	Elderly group ($N = 8$) Mean	SD	Probability (young vs. elderly)
Peroral dose (mg)	367.3	32.3	345.7	56.5	NS
Peroral dose (mg/kg)	4.94	0.10	4.91	0.19	NS
I.v. dose (mg)	362.3	47.3	350.1	46.9	NS
I.v. dose (mg/kg)	4.86	0.32	4.99	0.31	NS
AUC_{po} ($\mu g \cdot min \cdot ml^{-1}$)	3738.5 (3785.8)[a]	1491.5 (1508.8)[a]	3683.2 (3706.7)[a]	1921.4 (1774.4)[a]	NS
AUC_{iv} ($\mu g \cdot min \cdot ml^{-1}$)	3909.2 (3942.1)[a]	2038.4 (1737.4)[a]	3403.9 (3428.7)[a]	1246.1 (1292.2)[a]	NS
F(%)	108.8	12.7	102.8	6.3	NS
Time to peak[b] (t_{max}, min)	33.0	27.9	37.9	22.9	NS
Conc. at peak (C_{max}, min)	9.01 (9.08)[a]	2.9 (2.7)[a]	9.13 (9.28)[a]	1.6 (1.5)[a]	NS
Absorption rate constant (K_{01}, min^{-1})	0.3385	0.3716	0.1209	0.0590	NS
Absorption half-life[c] ($t_{1/2}$, K_{01}); min	2.05		5.73		
Absorption lag time (t_{lag}, min)	8.84	3.10	5.52	3.92	NS

[a] Values in parentheses have been adjusted to a dose of 5 mg/kg.
[b] Corrected for the absorption lag time.
[c] Calculated as the harmonic mean.

process was very rapid in both age groups, it should be noted that because of the rapidity of the absorption phase, insufficient plasma sampling points were obtained to characterize this process adequately, and hence the values of these parameters may be somewhat inaccurate. The rapid peroral absorption of caffeine from the aqueous solutions utilized resulted in an essentially complete bioavailability with average F(%) values of 108.8 and 102.8 in the young and elderly groups, respectively. The calculated values of F ranged from 94% to 130% but, again, the values for the two groups were not significantly different.

Although blood to plasma concentration ratios were not determined, if we assume that this ratio is unity, then an estimate of the hepatic first-pass metabolism of caffeine can be obtained. This assumption seems reasonable in view of reports that the blood to plasma ratio of the related xanthine, theophylline, is equal to unity (24,25). The mean steady-state extraction ratio (fraction lost during first-pass hepatic metabolism) equals blood metabolic (hepatic) clearance/hepatic blood flow. Assuming a liver blood flow of 1500 ml/min and using the values for CL_{NR} found in Table III, we obtain mean values of 0.0697 and 0.0742 for the young and elderly subjects,

Table III. Summary of Average Pharmacokinetic Parameters for Caffeine in Young and Elderly Men

Parameter	Young group ($N = 8$)	Elderly group ($N = 8$)	Probability (young vs. elderly)
$\lambda_z(\text{min}^{-1})_{iv}$	0.00234 (0.00085)[b]	0.00312 (0.00111)	NS
$\lambda_z(\text{min}^{-1})_{po}$	0.00270 (0.00091)	0.00319 (0.00127)	NS
$t_{1/2}, z(\text{min})_{iv}$[a]	296.2	222.2	
$t_{1/2}, z(\text{min})_{po}$[a]	256.7	217.3	
$fu(\%)$	64.34 (6.77)	65.03 (6.88)	NS
K/N (plasma); M	1.180×10^{-3}	1.089×10^{-3}	
Apparent V (ml/kg)[c]	613.0 (18.8)	524.1 (16.5)	$p < 0.01$
Apparent V_u (ml/kg)[c]	923.7 (89.8)	816.7 (74.1)	$p < 0.05$
$t_{1/2}, \lambda_1(\text{min})$[a,c]	8.87[d]	11.62[e]	
$t_{1/2}, k_{21}(\text{min})$[a,c]	19.17[d]	17.99[e]	
CL (ml/hr/kg)[c]	85.35 (28.09)	96.29 (29.37)	NS
CL_u (ml/hr/kg)[c]	128.48 (42.87)	153.12 (54.65)	NS
CL_R (ml/hr/kg)[c]	0.93 (0.24)	1.06 (0.48)	NS
CL_{R_u} (ml/hr/kg)[c]	1.40 (0.38)	1.69 (0.83)	NS
CL_{NR} (ml/hr/kg)[c]	84.42 (28.13)	95.22 (29.11)	NS
CL_{NR_u} (ml/hr/kg)[c]	127.08 (42.94)	151.43 (54.13)	NS
Caffeine excretion $Ae(0\text{–}24)(\text{mg})_{iv}$	4.21 (2.35)	3.65 (1.06)	NS
Caffeine excretion $Ae(0\text{–}24)(\text{mg})_{po}$	4.17 (1.63)	6.21 (6.95)	NS
Caffeine excretion$_{iv}$ (% of dose, % Ae)	1.12 (0.46)	1.07 (0.36)	NS
Caffeine excretion$_{po}$ (% of dose, % Ae)	1.13 (0.41)	1.89 (2.29)	NS

[a] Calculated as the harmonic mean.
[b] Values in parentheses represent one standard deviation.
[c] These parameters were calculated using intravenous data only.
[d] Based upon $N = 3$.
[e] Based upon $N = 2$.

respectively. Thus approximately 93% of a peroral dose would be expected to reach the systemic circulation intact.

The remaining pharmacokinetic parameters, describing the distribution and elimination of caffeine, are shown in Table III. The first item to note here is that the mean λ_z values in the elderly group are somewhat higher

than those measured in the young subjects. In addition, the mean λ_z values for the peroral and intravenous treatments are much closer in magnitude in the elderly subjects than they are in the young group. However, none of these differences were statistically significant. The result is that the half-lives are somewhat longer and more variable between treatments in the young subjects. The half-lives in the elderly group varied from 136 to 521 min following the intravenous dose and from 152 to 468 min following the oral dose. In the young group, the half-lives varied from 163 to 550 min following intravenous dosing and from 179 to 592 min following oral dosing.

The apparent volume of distribution for total drug (V) was also significantly higher ($p < 0.01$) in the young group. The mean plasma clearance of total drug (CL) is smaller and slightly less variable in the young group. The average renal clearance of unmetabolized total caffeine was low and similar between the two groups, with the result that the mean metabolic clearances closely paralleled the total body clearances. None of these differences reached statistical significance. The values of clearance (CL_u) and apparent volume of distribution (V_u) corrected for the degree of plasma binding exhibited the same trends as the uncorrected values between the subject groups as well as within a given subject group. This is not surprising in view of the close similarity of the mean values for the percent of caffeine unbound, $fu(\%)$, and the dissociation constant for the binding expressed in moles/liter (K/N) in both groups, shown in Table III. The quantities of caffeine excreted unchanged in the 24 hr following dosing, $Ae(0\text{–}24)$, averaged 1 to 2% of the dose.

Following the peroral dose, data from one elderly and one young subject were best described by a two-compartment model, while after the intravenous dose, data from two elderly and three young subjects were best fitted by a two-compartment model. All other data were described adequately by a one-compartment model. Only subject SS exhibited data which were best described by the two-compartment model following both peroral and intravenous dosing, as shown in Fig. 3.

DISCUSSION

The present study illustrates several aspects of the comparative pharmacokinetic behavior of caffeine in a young and an elderly group of healthy, active male subjects. The first point to note is that a 5 mg/kg dose of caffeine given either as a bolus perorally or as an intravenous infusion over 30 min produced no substantive alterations in the blood pressure, pulse rate, or electrocardiogram of the subjects. These observations, together with the subjective responses of our volunteers, indicate that this dose of caffeine is safe and produces no major undesirable side effects in either

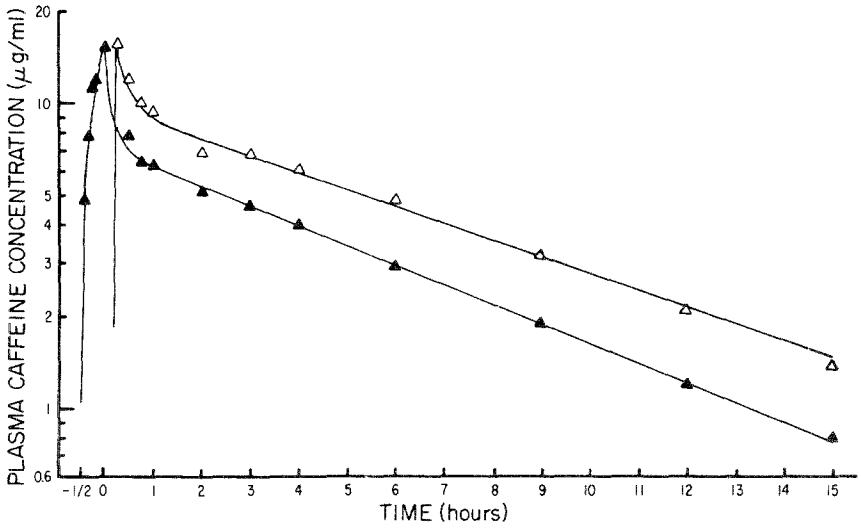

Fig. 3. Semilogarithmic plot of plasma caffeine concentration vs. time data in subject SS (age 23.3 years) following peroral (△—△) and intravenous (▲—▲) doses of 5.17 and 4.88 mg/kg caffeine, respectively. The peroral dose was given 10 days after the intravenous dose.

age group. The creatinine clearance data support some previous observations of Kampmann and Molholm Hansen (26), who noted that the creatinine clearance decreases with age.

Caffeine is absorbed rapidly and completely in both age groups following its administration perorally as an aqueous solution, as indicated by the t_{max}, C_{max}, K_{01}, t_{lag}, and $F(\%)$ values, which did not differ significantly between the two age groups. Previous reports have indicated that caffeine administered perorally to rats is subject to first-pass metabolism (27,28). However, in view of the essentially complete peroral absorption of caffeine observed in this study, this does not appear to occur in humans. This is illustrated by the close similarity of the mean plasma concentration versus time curves following peroral and intravenous administration of essentially identical doses of caffeine, shown in Figs. 1 and 2. These figures also illustrate the similarity of the pharmacokinetic behavior of caffeine in the two age groups.

Caffeine has also been reported to exhibit dose-dependent kinetics in rats at relatively low (≤ 10 mg/kg) peroral doses (27,28). This behavior apparently is not observed in other species including mice, rats, cynomolgus monkeys, and man (29,30). In all of the subjects studied here, the elimination of caffeine in the postabsorptive and/or postdistributive phases was log-linear following both peroral and intravenous administration. Other

workers have shown that the disappearance of caffeine from the plasma of adults (9,11) and infants (31,32) at doses comparable to the dose used here obeys first-order kinetics. While none of these single-dose studies (including this one) proves conclusively that caffeine pharmacokinetics in man are not dose-dependent, a recent study by Newton *et al.* (33) employing peroral doses of 50, 300, 500, and 750 mg indicated that caffeine obeys linear pharmacokinetics in man over this dose range.

While reductions in the gastrointestinal absorption of some compounds with aging have been reported (34,35), no such reduction was observed for caffeine in this investigation. Caffeine is a lipophilic molecule which readily penetrates biological membranes, and hence it is not too surprising that it is absorbed rapidly and completely. What was somewhat surprising was the extreme rapidity of the absorption following the peroral dose, with the result that for several subjects the peak plasma concentration (C_{max}) was reached before or shortly after the first plasma sampling point. This meant that for a few subjects, it was difficult to characterize the plasma concentration-time curve in the region near C_{max}. To alleviate this problem, additional samples were collected at 5 and 10 min after oral dosing in some of the subjects studied toward the end of this investigation.

The average apparent volumes of distribution (for both free and total drug) observed here were significantly lower in the elderly subjects. This observation is consistent with the general reduction in total body water and lean muscle mass (36) accompanying aging, and the fact that caffeine reportedly distributes freely into total body water (9). The average apparent volume of distribution of total drug observed in our young group (613.0 ml/kg) compares favorably with the value previously reported (11) for young, healthy subjects (610 ± 80 ml/kg).

The mean plasma clearance of total drug in our young group (85.35 ml/hr/kg) was somewhat lower than that observed in our elderly group (96.29 ml/hr/kg). This latter figure is very close to the value observed by Parsons and Neims (11) in 13 young, healthy, nonsmoking subjects. The average renal clearance of caffeine observed here was 0.93 ml/hr/kg in the young group and 1.06 ml/hr/kg in the elderly group, corresponding to a mean urinary excretion of unchanged caffeine equal to 1.13% of the dose in the 24 hr after dosing. This value is consistent with previous observations that 1–2% of a dose of caffeine is excreted unchanged (9,10). The metabolic clearance of caffeine was higher in the elderly group, indicating that the oxidative metabolic capabilities of their livers were, on the average, slightly greater than those of their younger counterparts. However, these small differences were not statistically significant.

The metabolism of caffeine in man is complex, involving primarily successive N-demethylations to form di- and monomethylated xanthines,

followed by oxidation at C-8 to form uric acid derivatives. These oxidative biotransformations occur primarily in the liver and proceed via the microsomal cytochrome P_{450} monooxygenases (37). Caffeine is known to be a particularly good substrate for cytochrome P_{448} (38), and it has been proposed that the delayed maturation of caffeine metabolism in the human neonate may be related to a particularly slow rate of development of this pathway relative to other functions of the hepatic monooxygenase system (37). While recent studies have helped to elucidate the complexities of the metabolism of caffeine in neonatal (37) and adult humans (39), there have been no studies to date which have examined whether there are any metabolic differences between young and elderly humans. Such differences would not be unexpected in view of previous studies examining the effect of aging on hepatic elimination (40). One recent study involving the related xanthine theophylline, which shares some common metabolic pathways with caffeine, indicated that both N-1 demethylation and C-8 oxidation may be less viable in the elderly (41).

The fairly wide range of biological half-lives and clearances observed in the present investigation probably reflects variations in the hepatic elimination of caffeine since about 98–99% of the caffeine filtered at the glomerulus is reabsorbed (42). The range of caffeine half-lives observed in this study (i.e., 2.27 to 9.87 hr) is consistent with those reported by Parsons and Neims (11) for 13 young, healthy, nonsmokers (i.e., mean, 6.0 hr; range, 3.0–9.4 hr). The difference in the half-lives between the two subject groups is probably a reflection of the differences in their volumes of distribution and clearance, which in concert determine the half-life.

The metabolic clearance of unbound drug (i.e., CL_{NR_u}), is a better reflection of the metabolic capacity of the liver than the total metabolic clearance (CL_{NR}) (43). The implicit assumption used in calculating the CL_{NR_u} is that the binding of caffeine to plasma protein is constant with time and independent of concentration in a given subject (44). These assumptions were checked and found to be valid (16). Although caffeine is, on the average, only about 35% bound to plasma protein in the subjects studied (16), the drug clearances and apparent distribution volumes could be influenced by interindividual differences in the unbound fraction. Thus, it was felt that the parameters for unbound clearance and apparent volume of distribution of caffeine would be a better indication of its clearance and distribution than those based upon total drug measurements (45). When the metabolic clearances of unbound caffeine in the two age groups were compared, the results were similar to those observed when metabolic clearances of total drug were compared in that no significant age-related differences were observed. These results indicate that the plasma protein

binding of caffeine is similar enough in both age groups so as not to be a major determinant of the metabolic clearance of caffeine.

The corrected apparent volumes of distribution, like the uncorrected values, were significantly lower ($p < 0.05$) in the elderly subjects. However, the differences in the corrected values between the two groups were somewhat less marked, indicating that some of the differences in the uncorrected values may have been due to interindividual differences in the plasma binding of caffeine. However, these results again confirm the fact that the plasma protein binding of caffeine does not exert a substantial influence on the distribution pattern of caffeine in young or elderly men.

In conclusion, it appears that most aspects of the pharmacokinetic behavior of caffeine are very similar in young and elderly males, with the one major difference being the reduced apparent volume of distribution in the elderly. This similarity is probably due, in large part, to the rigid criteria used for subject selection and the willing compliance of our subjects with the instructions given to them. In addition, a drug like caffeine, which is rapidly and completely absorbed and readily distributes throughout the body, may be less than optimal for characterizing the relatively small differences that often seem to exist between the types of subjects appropriate for investigating age-related aspects of pharmacokinetics; i.e., healthy, active, medication-free, and compliant (46,47). Since health and level of activity appear to play a much more important role than chronologic age in altering bodily functions, including pharmacokinetics, it may be more fruitful to develop and utilize indices of aging other than chronology in making such comparisons.

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REFERENCES

1. J. F. Greden. Coffee, tea and you. *The Sciences* **19**:6–11 (1979).
2. J. M. Ritchie. Central nervous system stimulants, the xanthines. In: L. S. Goodman and A. Gilman (eds.), *The Pharmacologic Basis of Therapeutics*, fifth ed. Macmillan, New York, 1975, pp. 367–378.

3. D. A. Holloway. Drug problems in the geriatric patient. *Drug Intell. Clin. Pharm.* **8**:332–342 (1974).
4. A. D. Bender. Pharmacodynamic principles of drug therapy in the aged. *J. Am. Geriatr. Soc.* **22**:269–303 (1974).
5. J. W. Gorrod. Absorption, metabolism and excretion of drugs in geriatric subjects. *Geront. Clin.* **16**:30–42 (1974).
6. E. J. Triggs and R. L. Nation. Pharmacokinetics in the aged: a review. *J. Pharmacokin. Biopharm.* **3**:387–418 (1975).
7. J. Crooks, K. O'Malley, and I. H. Stevenson. Pharmacokinetics in the elderly. *Clin. Pharmacokin.* **1**:280–296 (1976).
8. A. Aldridge, J. V. Aranda, and A. H. Neims. Caffeine metabolism in the newborn. *Clin. Pharmacol. Ther.* **25**:447–453 (1979).
9. J. Axelrod and J. Reichenthal. The fate of caffeine in man and a method for its estimation in biological material. *J. Pharmacol. Exp. Ther.* **107**:519–523 (1953).
10. H. H. Cornish and A. A. Christman. A study of the metabolism of theobromine, theophylline, and caffeine in man. *J. Biol. Chem.* **218**:315–323 (1957).
11. W. D. Parsons and A. H. Neims. Effect of smoking on caffeine clearance. *Clin. Pharmacol. Ther.* **24**:40–45 (1978).
12. J. M. Trang, J. Blanchard, K. A. Conrad, and G. G. Harrison. Effect of vitamin C on the pharmacokinetics of caffeine in elderly men. *Am. J. Clin. Nutr.* **35**:487–494 (1982).
13. J. Blanchard, J. D. Mohammadi, and K. A. Conrad. Improved liquid-chromatographic determination of caffeine in plasma. *Clin. Chem.* **26**:1351–1354 (1980).
14. J. Blanchard, J. D. Mohammadi, and J. M. Trang. Elimination of a potential interference in assay for plasma caffeine. *Clin. Chem.* **27**:637–639 (1981).
15. M. Jaffé, Ueber den niederschlag welchen pikrinsaure in normalem harn erzeugt und über eine neue reaction des kreatinins. *Hoppe Seylers Z. Physiol. Chem.* **10**:391–400 (1886).
16. J. Blanchard, Plasma protein binding of caffeine in young and elderly men. *J. Pharm. Sci.*, **71**:1415–1418 (1982).
17. J. A. Nelder and R. Mead. A simplex method for function minimization. *Computer J.* **7**:308–313 (1965).
18. J. H. Ottaway. Normalization in the fitting of data by iterative methods. *Biochem. J.* **134**:729–736 (1973).
19. H. G. Boxenbaum, S. Riegelman, and R. M. Elashoff. Statistical estimations in pharmacokinetics. *J. Pharmacokin. Biopharm.* **2**:123–148 (1974).
20. D. S. Riggs. *The Mathematical Approach to Physiological Problems.* Williams and Wilkins, Baltimore, 1963, p. 51.
21. M. Gibaldi and D. Perrier. *Pharmacokinetics.* Marcel Dekker, New York, 1975.
22. R. A. Upton, S. Riegelman, and L. B. Sheiner. Bioavailability assessment as influenced by changes in drug disposition. In: K. S. Albert (ed.), *Drug Absorption and Disposition: Statistical Considerations.* Am. Pharm. Assoc., Washington, D.C., 1980, pp. 77–86.
23. Anon. *Scientific Tables*, K. Diem and C. Lentner (eds.), Ciba-Geigy, Basel, 1970, p. 711.
24. M. Sheehan and P. Haythorn. Rapid gas-chromatographic determination of underivatized theophylline in whole blood. *J. Chromatogr.* **117**:393–398 (1976).
25. M. A. Peat and T. A. Jennison. Analysis of theophylline in serum and whole blood samples by high-pressure liquid chromatography. *J. Analyt. Toxicol.* **1**:204–207 (1977).
26. J. P. Kampmann and J. E. Molholm Hansen. Renal excretion of drugs. In: *Drugs and the Elderly—Perspectives in Geriatric Clinical Pharmacology.* University Park Press, Baltimore, 1979, pp. 77–87.
27. A. Aldridge, W. D. Parsons, and A. H. Neims. Stimulation of caffeine metabolism in the rat by 3-methylcholanthrene. *Life Sci.* **21**:967–974 (1977).
28. R. Latini, M. Bonati, D. Castelli, and S. Garattini. Dose-dependent kinetics of caffeine in rats. *Toxicol. Lett.* **2**:267–270 (1978).
29. S. Garattini. Third international caffeine workshop. *Nutr. Rev.* **39**:183–191 (1981).
30. R. Latini, M. Bonati, E. Marzi, M. T. Tacconi, B. Sadurska, and A. Bizzi. Caffeine disposition and effects in young and one-year old rats. *J. Pharm. Pharmacol.* **32**:596–599 (1980).

31. W. D. Parsons, J. V. Aranda, and A. H. Neims. Elimination of transplacentally acquired caffeine in full-term neonates. *Pediatr. Res.* **10**:333 (1976).
32. J. V. Aranda, W. Gorman, E. W. Outerbridge, and A. H. Neims. Pharmacokinetic disposition of caffeine in premature neonates with apnea. *Pediatr. Res.* **11**:414 (1977).
33. R. Newton, L. J. Broughton, M. J. Lind, P. J. Morrison, H. J. Rogers, and I. D. Bradbrook. Plasma and salivary pharmacokinetics of caffeine in man. *Eur. J. Clin. Pharmacol.* **21**:45–52 (1981).
34. M. Essam Fikry and M. H. Aboul-Wafa. Intestinal absorption in the old. *Geront. Clin.* **7**:171–178 (1965).
35. D. P. Richey and A. D. Bender. Pharmacokinetic consequences of aging. *Annu. Rev. Pharmacol. Toxicol.* **17**:49–65 (1977).
36. I. S. Edelman and J. Liebman. Anatomy of body water and electrolytes. *Am. J. Med.* **27**:256–277 (1959).
37. J. V. Aranda, J. L. Brazier, A. T. Louridas, and B. I. Sasyniuk. Methylxanthine metabolism in the newborn infant. In: L. F. Soyka and G. P. Redmond (eds.), *Drug Metabolism in the Immature Human*. Raven Press, New York, 1981, pp. 183–198.
38. H. Wietholtz, M. Vogelin, M. J. Arnaud, J. Bircher, and R. Preisig. Assessment of the cytochrome P-448 dependent liver enzyme system by a caffeine breath test. *Eur. J. Clin. Pharmacol.* **21**:53–59 (1981).
39. M. M. Callahan, R. S. Robertson, M. J. Arnaud, A. R. Branfman, M. F. McComish, and D. W. Yesair. Human metabolism of [1-methyl-^{14}C]- and [2-^{14}C] caffeine after oral administration. *Drug Metab. Dispos.* **10**:417–423 (1982).
40. U. Klotz and G. R. Wilkinson. Hepatic elimination of drugs in the elderly. In: K. Kitani, (ed.), *Liver and Aging*. Elsevier/North Holland Biomedical Press, New York, 1978, pp. 367–380.
41. E. J. Antal, P. A. Kramer, S. A. Mercik, D. J. Chapron, and I. R. Lawson. Theophylline pharmacokinetics in advanced age. *Br. J. Clin. Pharmacol.* **12**:637–645 (1981).
42. A. H. Neims. Third international caffeine workshop. *Nutr. Rev.* **39**:183–191 (1981).
43. G. R. Wilkinson and D. G. Shand. A physiological approach to hepatic drug clearance. *Clin. Pharmacol. Ther.* **18**:377–390 (1975).
44. D. G. Greenblatt, M. Divol Allen, J. S. Harmatz, and R. I. Shader. Diazepam disposition determinants. *Clin. Pharmacol. Ther.* **27**:301–312 (1980).
45. J. G. Wagner. Simple model to explain effects of plasma protein binding and tissue binding to calculated volumes of distribution, apparent elimination rate constants and clearances. *Eur. J. Clin. Pharmacol.* **10**:425–432 (1976).
46. R. E. Schneider, H. Bishop, R. A. Yates, C. P. Quarterman, and M. J. Kendall. Effect of age on plasma propranolol levels. *Br. J. Clin. Pharmacol.* **10**:169–170 (1980).
47. D. G. Greenblatt and R. I. Shader. Effects of age and other drugs on benzodiazepine kinetics. *Arzn. Forsch.* **30**:886–890 (1980).