The effect of vitamin C on the pharmacokinetics of caffeine in elderly men[1-3]

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ABSTRACT The influence of vitamin C on the pharmacokinetics of caffeine was investigated in 10 elderly males, age 66 to 86 yr. Caffeine was administered intravenously on three different occasions over a 7-wk period: before vitamin C restriction, after approximately 4 wk of vitamin C restriction (15 mg dietary intake per day), and after 2 wk of vitamin C supplementation (500 mg orally, twice daily). Blood and urine samples were collected over a 48-h period after each caffeine administration. The plasma half-life, rate constant of elimination, apparent volume of distribution, total body clearance, renal clearance, and metabolic clearance of caffeine were determined. Simultaneous plasma, whole blood and leukocyte vitamin C concentrations were obtained. All of the average vitamin C concentrations monitored (plasma, whole blood, and leukocyte) changed significantly during the study, corresponding to the alterations in dietary vitamin C intake. Conversely, none of the caffeine pharmacokinetic parameters evaluated changed significantly during the study. The average metabolic clearance was approximatley 77 (ml hr^{-1}) kg^{-1} and the average half-life was approximately 4.6 h for all caffeine administrations. These results indicate that the elimination of caffeine in the elderly is not affected significantly by the concentrations of vitamin C achieved during this study. *Am J Clin Nutr* 1982; 35:487–494.

KEY WORDS Vitamin C, caffeine, pharmacokinetics, elderly, males

Introduction

The elderly comprise an ever increasing segment of the population and are unusually susceptible to adverse drug reactions (1). This increased susceptibility to adverse drug reactions may in part be attributable to age-related changes in the pharmacokinetics of drugs which can ultimately affect their pharmacological action and toxicity.

The elderly often have lower than normal plasma levels of essential nutrients compared to the accepted values for young adults (2), however, the significance of the "lower than normal" values is not well established. Nutritional deficiencies have been shown to affect the kinetics of many drugs directly by altering their metabolism (3). Specifically, vitamin C has been shown to influence the oxidative metabolism of a variety of drugs (4), including some oxidative demethylation processes in guinea pigs (5). Although caffeine is a very commonly used drug, which is metabolized by oxidative processes, no relationships between vitamin C and caffeine metabolism have been reported for laboratory animals or humans.

The overall objective of this study was to investigate the influence of vitamin C on the pharmacokinetics of caffeine in healthy elderly men. Caffeine was selected for this study for two major reasons. First, it is widely used in over-the-counter analgesic preparations, it is present in coffee, tea, and many carbonated beverages, and it is consumed on a daily basis by a large proportion of the population, including the elderly. Second, it is eliminated (≥98%) from the plasma primarily via two oxidative metabolic pathways, demethylation and oxidation, that may be altered in the elderly.

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Methods

Caffeine was administered intravenously to 10 elderly men on three separate occasions, corresponding to three different levels of vitamin C intake. Each caffeine administration and the collection of blood and urine samples will hereafter be referred to as a kinetic trial (KT). The first kinetic trial (KT-1) was conducted before any alteration in diet or intervention with supplemental vitamin C. The second kinetic trial (KT-2) was conducted after approximately 4 wk of dietary vitamin C restriction. The third kinetic trial (KT-3) was conducted after 2 wk of vitamin C supplementation. The procedures followed were in accord with the ethical standards of the Human Subjects Committee of the University of Arizona.

Ten subjects ranging in age from 66 to 86 yr (average 72 yr) were identified from the local geriatric population and were assessed as "healthy" on the basis of a normal health history, physical examination, chest x-ray, and ECG. In addition, all subjects were within normal limits with respect to the following laboratory tests: serum calcium, phosphorus, uric acid, glucose, cholesterol, albumin, bilirubin, alkaline phosphatase, creatinine, and SGOT; hematocrit; Hb; white blood cell count with differential and platelet adequacy; creatinine clearance; and urinary pH, speciffic gravity, albumin, glucose, color, ketones, and occult blood. All subjects were within 15% of the average body weight for their respective height, when compared to men age 60 to 69 yr (6). None of the subjects smoked or used tobacco-containing products, and all were light to moderate coffee or tea drinkers (i.e., $\leq$ 3 cups/day). None had consumed alcoholic beverages within 1 month before the study, and none was receiving any prescription medication. With the exception of one subject who took two aspirin tablets (650 mg) on a daily basis, no nonprescription medications were consumed.

In addition to the physical examination each subject underwent a dietary evaluation (i.e., a dietary history, a 24-h recall of food intake, a food frequency questionnaire, and a 72-h food intake record) and the measurement of plasma (PVC), whole blood (WBVC), and leukocyte (LVC) vitamin C levels. Since our LVC assay utilized a buffy coat, the LVC values actually represent the sum total of the concentrations present in the leukocytes and platelets combined. Dietary restrictions of coffee, tea, and other caffeine-containing beverages and foods were instituted 72 h before each kinetic trial, and continued until 48 h after each caffeine administration. Dietary control of each subject's vitamin C intake was instituted immediately after the conclusion of KT-1 and was continued throughout the study at a level of approximately 15 mg of vitamin C per day. Vitamin supplementation with a multiple vitamin (Centrum tablets without vitamin C, Lederle Laboratories Division, American Cyanamid Company, Pearl River, NY) formulated specifically for this study, containing 20 essential vitamins and minerals except vitamin C, was instituted at the same time as the vitamin C-restricted diet and was continued throughout the study. This insured that each subject received at least the recommended daily allowance of most essential vitamins and minerals (except for vitamin C) and that any observed changes in the metabolism of caffeine in these subjects after supplementation with vitamin C would not be confounded by low dietary intakes of these other nutrients. Vitamin C supplementation, 1 g/day in divided doses, was instituted 48 h after the second kinetic trial using a 250 mg chewable tablet (Roche Chemical Division, Hoffmann-La Roche Inc., Nutley, NJ) and was continued until the conclusion of KT-3, 2 wk later. A 72-h food intake record was obtained for the 3 days immediately preceeding each kinetic trial and an approximate daily vitamin C intake (DVCI) was calculated.

All doses of caffeine were administered intravenously at approximately 9:00 AM on the day of each of the three kinetic trials. A 4 mg kg^{-1} dose of caffeine (Caffeine and Sodium Benzoate Injection, U.S.P., Eli Lilly and Company, Indianapolis, IN) was diluted with approximately 30 ml of Bacteriostatic Sodium Chloride Injection, U.S.P. (Abbott Laboratories, North Chicago, IL) and administered over 20 to 30 min via a heparin lock placed in a forearm vein. The infusion syringe was rinsed with an additional 15 ml of Bacteriostatic Sodium Chloride Injection, U.S.P., and then flushed through the lock to ensure administration of the entire dose. Blood pressure and pulse rate were monitored before, during, and after the infusion. Additional blood pressures and pulse rates were monitored at the time of each blood collection, up to and including the 12-h sample.

During each kinetic trial, individual 5-ml blood samples were withdrawn for caffeine determination from the same heparin lock through which the caffeine was administered. A sample was collected before each dose of caffeine, and at the following times postinfusion: 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 9, 12, 15, 19, and 23 h. The heparin lock was then removed and individual 5-ml samples were collected by venipuncture at times 30 and 46 h. An additional 15 to 20-ml blood sample was collected with the 23-h sample for vitamin C assay. All blood samples collected for caffeine determination were centrifuged for 15 min at 2000 $\times$ g within 4 h after collection. After centrifugation, the plasma was harvested, refrigerated immediately, stored at -4°C within 24 h, and assayed within 30 days. Blood samples for vitamin C determination were processed within 2 h of collection. Additional blood samples for vitamin C determination were collected at weekly intervals during the period of dietary vitamin C restriction and supplementation.

Before the administration of caffeine, each subject was instructed to empty his bladder completely and a 20-ml aliquot of urine was collected for the determination of pH. Total urine collections were made for two 24-h periods after caffeine administration. Urine samples were refrigerated for a maximum of 48 h at which time their volumes were measured and a 20-ml aliquot was stored at -4°C for assay within 60 days.

Caffeine in plasma samples from KT-1 was quantitated using a high-performance liquid chromatographic technique developed by Blanchard, et al (7). A solvent extraction method analogous to one described earlier for plasma was used to separate caffeine from all urine samples before quantitation. Plasma samples from KT-2 and KT-3 and all urine samples were assayed for caffeine by a modification of the above method (8).

For plasma vitamin C determinations 1.0 ml aliquots of plasma were precipitated with equal volumes of cold, 5% w/v trichloroacetic acid (TCA). Whole blood samples were homogenized in a glass, hand-held Potter-Elvehjem homogenizer before precipitation with twice their vol-

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ume of cold 5% w/v TCA. Samples for leukocyte vitamin C determination were prepared by a modification of the method of Marchand and Pelletier (9). After separation, the leukocyte and platelet-rich pellet obtained was homogenized with 1.5 ml of cold, 5% w/v TCA. Before homogenization an aliquot of each sample was taken for manual leukocyte (WBC) counting using a hemacytometer (American Optical Corporation, Buffalo, NY). To prevent adhesion of leukocytes and platelets, all glassware used in the preparation of LVC samples was silanized by soaking in a mixture of dimethylsilane in toluene (5% v/v) for 15 to 30 min. After precipitation with TCA all samples were placed on ice for 10 min and then centrifuged at 1800 × g for 10 min. The vitamin C content in all samples was determined by a modification of the spectrophotometric procedure outlined by Baker and Frank (10). PVC and WBVC concentrations were expressed in mg/100 ml and LVC concentrations in μg $(10^8 \text{ WBC})^{-1}$. Since LVC concentration is inversely related to the total WBC count (11), each WBC level was normalized to a WBC count of 4000 WBC $(\text{mm}^3)^{-1}$, hereafter referred to as normalized leukocyte vitamin C concentration (NLVC).

Caffeine plasma concentration versus time data were fitted to both a one- and a two-compartment open model using a nonlinear regression technique, NONLIN (12), and a logarithmic weighting factor. The 0-, 0.25-, and 0.5-h samples were not included in the analysis because of the potential contamination of these samples with administered caffeine solution. A statistical evaluation to determine the most appropriate compartmental model was performed using the method of Boxenbaum et al. (13). All data sets were described adequately using a monoexponential, one-compartment model. A zero-time intercept (C_0) and elimination rate constant (K) were obtained from the NONLIN computer printout. From these two parameters a half-life ($t_{1/2}$) and a corrected zero-time intercept (C_0^*) were calculated using the following equations (14):

$$t_{1/2} = \frac{0.693}{K} \qquad (1)$$

and

$$C_0^* = \frac{(C_0)(X_0)(K)}{(K_0)(1 - e^{-KT})} \qquad (2),$$

where X_0 is the intravenous dose, K_0 is the infusion rate, and T is the infusion time. From the corrected zero-time intercept and the elimination rate constant the total area under the plasma caffeine concentration versus time curve AUC_0^∞ was calculated using the following equation:

$$AUC_0^\infty = \frac{C_0^*}{K} \qquad (3).$$

When the blank plasma caffeine concentration (C_{B1}) for a given subject was greater than 0.6 μg ml^{-1}, the total urea under the curve was corrected by subtracting the area contributed by this initial plasma caffeine concentration using the following equation:

$$AUC_0^\infty = \frac{C_0^*}{K} - \frac{C_{B1}}{K} \qquad (4).$$

From the above parameters the apparent volume of distribution (V) and the total body clearance (TBC) were calculated using the following equations:

$$V = \frac{X_0}{(K)(AUC_0^\infty)} \qquad (5)$$

and

$$TBC = \frac{X_0}{AUC_0^\infty} \qquad (6).$$

Although timed urine collections were made for the 0- to 23-h and 23- to 47-h periods after each caffeine administration, the caffeine concentrations in the 23- to 47-h urine samples were consistently below the 0.6 μg ml^{-1} limit previously determined to be the minimum concentration required for accurate quantitation. Consequently, the renal clearance (RC) was calculated based upon a one-point determination using the following equation:

$$RC = \frac{Xu_0^{23}}{AUC_0^{23}} \qquad (7),$$

where Xu_0^{23} is the amount of caffeine excreted in the urine during the 0- to 23-h period and AUC_0^{23} is the area under the caffeine plasma concentration versus time curve from 0 to 23 h. Metabolic clearance (MC) was then calculated using the following equation:

$$MC = TBC - RC \qquad (8).$$

A variety of null hypotheses were tested using a single factor repeated measures design analysis of variance (ANOVA) developed by Specht and Hohlen (15). If this initial analysis demonstrated a statistically significant difference in a set of the three means for a given parameter ($p < 0.01$), three additional pair-wise analyses were tested using the same repeated measures ANOVA to determine whether the difference was between means one and two, two and three, and/or one and three. A p value of 0.0017 was required for these post hoc tests.

Results

Selected demographic and laboratory findings for each of the subjects are presented in **Table 1.** The average weight at the time of the entrance physical examination was 77.0 ± 8.5 kg. The average subject weight at KT-1, KT-2, and KT-3, was 77.9 ± 8.3, 77.6 ± 7.9, and 78.1 ± 8.2 kg, respectively. No significant change in weight occurred during the dietary vitamin C restriction and supplementation ($p = 0.4728$).

A summary of the average PVC, WBVC, and LVC concentrations for each of the kinetic trials is presented in **Table 2.** Average PVC, WBVC, and NLVC levels were significantly reduced for KT-2 compared to KT-1 ($p = 0.0001$), and were significantly elevated

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TABLE 1
Selected demographic and laboratory findings in elderly subjects (n = 10) at the time of the physical examination

Subject	Age*	Ht*	Wt*	Blood urea nitrogen*	Creatinine clearance†
	yr	*cm*	*kg*	*mg/100 ml*	*ml min^{-1} (1.73 m^2)$^{-1}$*
A	66	185	97	20	68
B	66	187	79	15	63
C	67	178	79	11	115
D	68	179	85	15	62
E	69	180	70	18	89
F	70	183	75	14	92
G	75	180	74	14	58
H	75	173	72	15	69
I	80	175	74	24	82
J	86	173	67	16	95
Average	72	179	77	16	79
SD	7	5	9	4	18

* Values at time of entrance physical examination.
† Values at time of discharge physical examination approximately eight weeks later. Each subject's body surface area was calculated using a nomogram (16).

TABLE 2
Summary of average PVC, WBVC, and LVC concentrations in elderly men (n = 10) for the three kinetic trials

Trial	Time on diet	Intake*	Plasma level	Whole blood level	Leukocyte level	Leukocyte count	Normalized leukocyte level†
	days	*mg*	*mg/100 ml*	*mg/100 ml*	*ug (10^6 WBC)$^{-1}$*	*WBC (mm^3)$^{-1}$*	*ug (10^6 WBC)$^{-1}$*
KT-1	−1	214	0.86	0.92	19.72	5,250	22.45
	(0)‡	(229)	(0.37)	(0.30)	(11.11)	(1,760)	(6.47)
KT-2	32	13	0.27	0.23	10.01	4,940	11.77
	(3)	(9)	(0.13)	(0.13)	(6.09)	(870)	(6.04)
KT-3	46	1038	1.55	1.55	26.85	3,670	24.32
	(3)	(70)	(0.36)	(0.31)	(7.79)	(550)	(6.69)
p, overall		0.0001§	0.0001§	0.0001§	0.0001§	0.0092§	0.0001§
p, KT-1 to KT-2		0.0203	0.0005§	0.0001§	0.0188	0.6218	0.0001§
p, KT-2 to KT-3		0.0001§	0.0001§	0.0001§	0.0001§	0.0006§	0.0001§
p, KT-1 to KT-3		0.0001§	0.0029	0.0015§	0.0449	0.0114	0.3630

* Average total daily vitamin C intake including vitamin supplementation based upon the 72-h food intake record.
† Leukocyte vitamin C level adjusted to a leukocyte count of 4000 WBC (mm^3)$^{-1}$.
‡ Values in parentheses indicate the SD.
§ Statistically significant difference; $p < 0.01$ for overall comparisons and $p < 0.0017$ for post hoc comparisons.

at KT-3 compared to the other two kinetic trials ($p = 0.0001$). Average LVC levels dropped less strikingly between KT-1 and KT-2 ($p = 0.0188$), but rose significantly from KT-2 to KT-3 ($p = 0.0001$). The average LVC levels at KT-3 were somewhat higher than for KT-1 ($p = 0.0449$). These data are consistent with the findings of other investigators (17–19), and correspond to the decrease in the daily vitamin C intake from KT-1 to KT-2 ($p = 0.0203$) and the increase from KT-2 to KT-3 ($p = 0.0001$). Normal leukocyte counts are generally in the range of 4,000 to 10,000 WBC (mm^3)$^{-1}$ of whole blood (20). Table 2 illustrates that the mean leukocyte counts at KT-1 and KT-2 were nearly identical ($p = 0.6218$) and within the normal range. The reduction in the mean leukocyte count from KT-2 to KT-3 ($p = 0.0006$) coincides with an increase in the daily vitamin C intake. The significance of this observation is uncertain.

The average intravenous caffeine pharmacokinetic data for each of the kinetic trials are summarized in **Table 3.** A typical caffeine plasma concentration versus time plot in one

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TABLE 3
Summary of average intravenous caffeine pharmacokinetic data in elderly men (n = 10) for the three kinetic trials

Trial	Elimination rate constant	Plasma $t_{1/2}$*	Apparent volume of distribution	Clearances [(ml h^{-1}) kg^{-1}]			Urinary caffeine excretion†	
				Total body	Renal	Metabolic	Amount	Percentage of dose
	h^{-1}	h	ml kg^{-1}				mg	
KT-1	0.1432	4.84	513	74.42	1.25	73.17	5.21	1.67
	(0.0505)‡		(39)	(30.25)	(0.63)	(29.68)	(1.42)	(0.42)
KT-2	0.1584	4.38	499	79.11	1.29	77.82	4.86	1.56
	(0.0547)		(33)	(28.54)	(0.60)	(28.12)	(1.64)	(0.53)
KT-3	0.1539	4.50	497	77.15	1.25	75.90	4.92	1.56
	(0.0617)		(30)	(33.18)	(0.61)	(32.69)	(1.79)	(0.48)
p, overall§	0.0582		0.3400	0.2551	0.9411	0.2526	0.7890	0.7694

* Average caffeine plasma $t_{1/2}$ calculated from the average elimination rate constant.
† Based upon urine collections during the first 23 h of each kinetic trial.
‡ Values in parentheses indicate SD.
§ No statistically significant differences were observed at the $p < 0.01$ level.

subject for all three kinetic trials is presented in **Figure 1.** A plot of the average caffeine plasma concentration versus time data for the three kinetic trials is presented in **Figure 2.** This plot was constructed using the average elimination rate constant (K) and the average corrected zero-time intercept (C_0*) for each kinetic trial. No statistically significant change occurred in the average elimination rate constant ($p = 0.0582$) or apparent volume of distribution ($p = 0.3400$). Similarly, no statistically significant change occurred in the average total body clearance ($p = 0.2551$), renal clearance ($p = 0.9411$), or metabolic clearance ($p = 0.2526$). Neither the average amount of caffeine excreted in the urine (Xu_0^{23}) nor the percentage of the dose (X_0) excreted during the first 23 h of each kinetic trial changed significantly ($p = 0.7890$ and 0.7694, respectively). Since there were no significant overall changes in any of these parameters, no pair-wise comparisons were made.

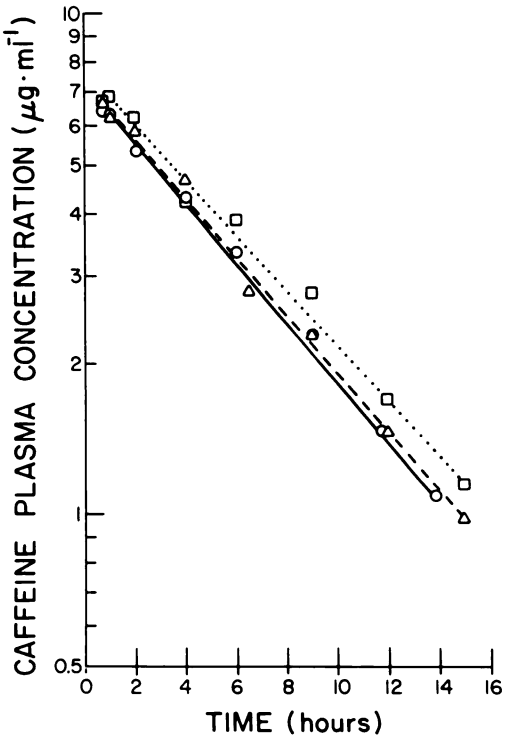

FIG. 1. Semilogarithmic plot of caffeine plasma concentration in one typical elderly subject as a function of time after an intravenous infusion of 4 mg kg^{-1} caffeine at three separate times corresponding to three different levels of vitamin C intake. Symbols represent: O——O, the first kinetic trial (KT-1) before any dietary vitamin C restriction; Δ---Δ the second kinetic trial (KT-2) after approximatley 4 wk of dietary vitamin C restriction; □. . .□ the third kinetic trial (KT-3) after 2 wk of dietary vitamin C supplementation.

Discussion

These results indicate that short-term alterations in dietary vitamin C intake do not affect caffeine metabolism in elderly men. These findings are consistent with the work of Wilson et al. (21) who studied the effects of vitamin C on the elimination of antipyrine in 14 healthy adults ranging in age from 24 to 45 yr. While that study did not investigate

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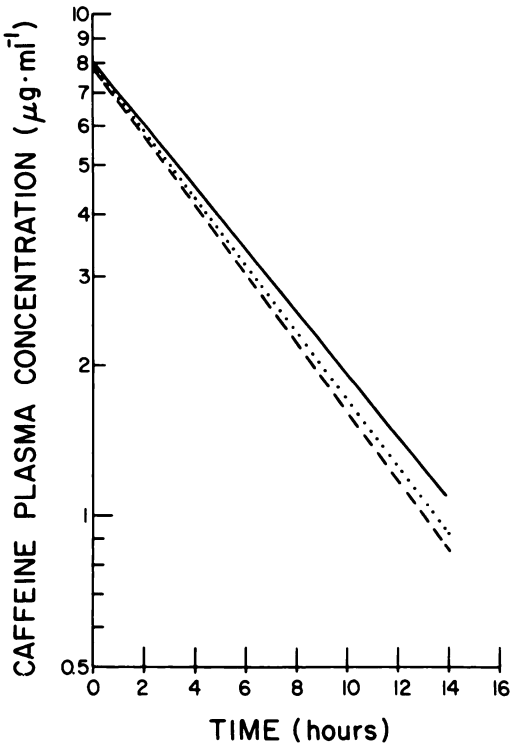

FIG. 2. Semilogarithmic plot of average caffeine plasma concentrations in elderly males (n = 10) as a function of time after an intravenous infusion of 4 mg kg^{-1} caffeine at three separate times corresponding to three different levels of vitamin C intake. *Solid line*, the first kinetic trial (KT-1) before any dietary vitamin C restriction; *dashed line*, the second kinetic trial (KT-2) after approximately 4 wk of dietary vitamin C restriction; and *dotted line*, the third kinetic trial (KT-3) after 2 wk of dietary vitamin C supplementation.

the influence of vitamin C depletion, it did investigate the effect of supplemental vitamin C (30 to 2400 mg/day) on antipyrine kinetics. These authors found that added vitamin C had no effect on the pharmacokinetics of antipyrine. In contrast, Houston (22) and Smithard and Langman (23, 24) observed an increased metabolic clearance of antipyrine after the administration of vitamin C to non-deficient young subjects and vitamin C-deficient elderly subjects. No indication was given in the above studies regarding whether any attempts were made to control the dietary intake of vitamin C or other compounds that could potentially influence the metabolism of antipyrine.

All of the mean vitamin C values determined at KT-1 were within the normal ranges for the respective biological fluid or tissue concentrations. Of the subjects, 20% had PVC, WBVC, and NLVC values below the normal range, and 50% of the subjects had LVC values below the normal range. Without exception, all of the mean vitamin C values changed significantly during the study. The mean PVC, WBVC, and NLVC decreased significantly between KT-1 and KT-2 after a period of dietary vitamin C restriction. The mean PVC, WBVC, LVC, and NLVC increased significantly between KT-2 and KT-3 after a period of vitamin C supplementation. The leukocyte counts at KT-1 and KT-2 were nearly identical, but decreased significantly from KT-2 to KT-3. In all instances the individual and mean vitamin C concentrations observed at KT-3 were higher than those observed at KT-1 and KT-2. All of the changes in the individual and mean vitamin C concentrations paralleled the observed changes in daily vitamin C intake, in agreement with the work of other investigators (17–19).

None of the changes in caffeine's pharmacokinetic parameters observed during the study were statistically significant. The values for K, $t_{1/2}$, and percentage of dose excreted unchanged in the urine, are in good agreement with values reported in younger subjects (25, 26). However, the mean V observed here (503 ml kg^{-1}), is about 17.5% lower than the value (610 ml kg^{-1}) reported for younger subjects (26). In addition, the mean TBC [77 (ml h^{-1})kg^{-1}] is about 18.2% lower than the value reported in younger subjects (25). The somewhat lower TBC observed here appears to be associated with the lower V in the elderly subjects. This may be due to the reported reduction in total body water with increasing age (27), since caffeine distributes freely into total body water (25).

Furthermore, Parsons and Neims (26) used saliva sampling after the oral administration of caffeine. Since the oral dose may not have been completely absorbed their TBC and V may have both been over estimated thereby reducing the actual differences between our results and theirs. However, it should be noted that factors other than age may have been responsible for the observed differences

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between the average pharmacokinetic parameters reported here and by Parsons and Neims (26). The considerable inter-subject variability in these parameters observed in both studies would require much greater numbers of subjects to establish such differences unequivocally.

The mean PVC, WBVC, and LVC all changed characteristically during the study, corresponding to the periods of dietary vitamin C restriction and supplementation. Since no statistically significant alterations in the average K, $t_{1/2}$, TBC, RC, and/or MC occurred during the same periods of dietary vitamin C restriction and supplementation, no relationship between vitamin C intake and/or body levels and the pharmacokinetics of caffeine can be established for the conditions utilized during this study. It should be noted that the dietary intake of vitamin C was well controlled and that compounds that could potentially affect the metabolism of caffeine were restricted during the study.

It is possible that vitamin C is not involved in the enzymatic demethylation of caffeine. However, since a substantial body of evidence indicates that oxidative demethylation reactions are influenced by vitamin C in animal models (5), it is possible that the decreases in vitamin C concentrations achieved during this study were not large enough to produce a significant change in the elimination of caffeine. All of the studies investigating the relationship between vitamin C and drug metabolism in guinea pigs have indicated that vitamin C depletion to near-scorbutic levels is required before any alteration in drug metabolism is observed. If this is true in humans, approximately 90 to 100 days of total dietary vitamin C restriction may be necessary before alterations in drug metabolism would be observed.

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