Effect of Caffeine on Circulating Theophylline Levels in Beagle Dogs

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Abstract □ The pharmacokinetic interactions of caffeine with theophylline were examined in two beagle dogs by administering 100 mg of aminophylline intravenously, 3 weeks before and immediately after repeated oral doses of caffeine. Serial plasma samples were analyzed for caffeine and theophylline simultaneously by high-performance liquid chromatography. Upon multiple oral dosing, 100 mg every 12 hr for 7 days, the caffeine half-life increased slightly in one dog but decreased in the other. As predicted from single-dose data, caffeine accumulation in plasma after repeated doses was slight, while plasma levels of the *N*-demethylated metabolite, theophylline, rose to about three times the initial values. After rapid intravenous doses of aminophylline, the theophylline half-life was 5–7 hr, which decreased slightly when the drug was administered concomitantly with caffeine during steady state of caffeine. The theophylline volume of distribution (0.75 liter/kg) was unaffected by caffeine. On the other hand, an acute aminophylline injection prolonged the elimination half-life and increased the apparent volume of distribution of caffeine, causing little overall change in its plasma clearance. The results suggested that interactions between theophylline and caffeine may be attributed to changes in drug distribution and drug elimination characteristics.

Keyphrases □ Caffeine—pharmacokinetic interactions with theophylline □ Theophylline—pharmacokinetic interaction with caffeine □ Plasma clearance—plasma caffeine levels, plasma theophylline levels

The bronchodilator theophylline is eliminated from the human body primarily by metabolism. Approximately 90% of the dose is metabolized by the liver *via* oxidative and demethylation reactions to 3-methylxanthine, 1,3-dimethyluric acid, and 1-methyluric acid (1). The plasma half-life of theophylline in humans is ~6 hr after intravenous (2) or oral (3) dosing, and kinetic indexes in asthmatics and healthy adults are similar (4).

The effect of concurrent administration of other drugs on theophylline disposition has been examined to some extent. Piafsky *et al.* (5) observed *in vivo* induction of theophylline metabolism in humans by phenobarbital, although others (6) reported decreased or unchanged theophylline clearance after phenobarbital therapy. Allopurinol, a xanthine oxidase inhibitor, blocks the conversion of 1-methylxanthine to 1-methyluric acid but has no significant effect on the overall theophylline clearance (7, 8).

In a recent study, Monks *et al.* (9) reported a decrease in the theophylline elimination half-life in subjects on a methylxanthine-free diet. These authors suggested that, since theophylline and the dietary methylxanthines share common metabolic pathways, they may compete with one another for the same enzymes, thus resulting in suppressed theophylline metabolism. On the other hand, caffeine was shown to increase enzyme synthesis in rat liver (10), which could enhance drug metabolism.

The present study concerned caffeine pharmacokinetics in the dog after single and multiple oral doses of caffeine tablets for 1 week. The effect of steady-state blood levels of caffeine on theophylline disposition was examined by administering aminophylline intravenously, 3 weeks before and immediately after the caffeine multiple-dosing regimen. Changes in the pharmacokinetic profile of caffeine due to an acute aminophylline injection were also analyzed.

EXPERIMENTAL

A 1-year-old male (Dog A, 11.4 kg) beagle dog and a 2-year-old female (Dog B, 11.7 kg) beagle dog were used. The dogs were fasted overnight before and 4 hr after each drug dose in the single-dosing experiments and the first and last dose in the multiple-dosing experiments. During an experiment, dogs were initially placed in a restraining sling to facilitate accurate drug administration and blood sample collection.

Single Intravenous Aminophylline—Each dog received a single 100-mg aminophylline[1] (85% theophylline) dose by bolus injection into a front leg vein. Serial 5-ml blood samples were collected in 10-ml heparinized tubes[2] during 24 hr after dosing. Plasma was separated by centrifugation and stored at −20° prior to assay.

Multiple Oral Caffeine—Multiple caffeine regimens were started 3 weeks after the initial aminophylline dose. Each dog received one 100-mg tablet of caffeine[3] twice daily at 9:00 am and 9:00 pm for 8 days. Tablets were administered by placing them on the posterior portion of the tongue so that they were not fractured before being swallowed and were followed by 5 ml of water. A predose blood sample was taken before each morning dose, and serial blood samples were collected during the 12 hr after the morning doses on Days 1 and 8.

Concurrent Aminophylline and Caffeine—On the day after the multiple caffeine experiments (Day 9), each dog received orally a 100-mg caffeine tablet at 9:00 am, followed immediately by an intravenous injection of 100 mg of aminophylline. Blood samples were collected immediately before and serially during 24 hr after dosing.

Plasma Assay—Plasma concentrations of theophylline and caffeine were determined in 1-ml samples by the high-performance liquid chromatographic (HPLC) assay of Valia *et al.* (11). Samples were prepared as described previously, but the chromatographic conditions were modified slightly. A 10-μm μBondapak C_{18} column[4] was used in conjunction with a chromatograph[5] equipped with a spectrophotometric detector[6]. The mobile phase was 10% acetonitrile–0.01 *M* acetate buffer (pH 4). The column temperature and the solvent temperature were ambient. A flow rate of 1.5 ml/min was used, yielding an operating pressure of 1500 psi. The spectrophotometric detector had a 15.6-μl cell volume and was operated at 280 nm.

[1] Aminophylline Injection USP, 25 mg/ml, Gibco/Invenex, Chagrin Falls, Ohio.
[2] Vacutainer, Becton-Dickinson, Rutherford, N.J.
[3] NoDoz, Bristol-Myers, New York, N.Y.
[4] Waters Associates, Milford, Mass.
[5] Model 244, Waters Associates, Milford, Mass.
[6] Model 440, Waters Associates, Milford, Mass.

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Table I—Pharmacokinetic Parameters of Caffeine after Single and Repeated Oral Doses

Parameter	Dog A		Dog B	
	Day 1	Day 8	Day 1	Day 8
k_a, hr^{-1}	1.29	0.71	1.76	0.72
	(−0.17–2.75)[a]	(0.45–0.97)	(0.79–2.74)	(0.19–1.25)
$t_{1/2,abs}$[b], hr	0.54	0.97	0.39	0.96
k_{el}, hr^{-1}	0.18	0.15	0.13	0.21
	(−0.013–0.37)	(0.11–0.20)	(0.067–0.20)	(0.086–0.34)
$t_{1/2}$[c], hr	3.84	4.52	5.16	3.23
FD/V, μg/ml	16.0	19.1	12.3	18.0
	(6.09–25.9)	(13.8–24.4)	9.34–15.3)	(7.80–28.2)
t_0, hr	0.083	—[d]	0.027	—
	(−0.10–0.27)		(0.062–0.12)	
r^2 [e]	0.82	0.96	0.94	0.91
$AUC^{0\to\infty}$[f], (μg hr)/ml	88.9	—	94.6	—
$AUC^{0\to12}$[g], (μg hr)/ml	—	122	—	83.8
C_{max}[h], μg/ml	11.6	15.6	9.97	12.0
t_{max}[i], hr	1.84	2.44	1.61	2.23

[a] The 95% confidence limits. [b] Half-time of absorption = $0.693/k_a$. [c] Half-life of elimination by all routes = $0.693/k_{el}$. [d] Not calculated. [e] Coefficient of determination = $(\Sigma \text{ obs}^2 - \Sigma \text{ dev}^2)/\Sigma \text{ obs}^2$. [f] Area under plasma level–time curve = FD/Vk_{el}. [g] Obtained by trapezoidal rule.

[h] Peak height:

$$\text{Day 1} = \frac{FD}{V}\left(\frac{k_a}{k_{el}}\right)^{k_{el}/(k_{el}-k_a)}$$

$$\text{Day 8} = \frac{FD}{V}\left(\frac{1}{1-e^{-k_{el}\tau}}\right)\left[\frac{k_a(1-e^{-k_{el}\tau})}{k_{el}(1-e^{-k_a\tau})}\right]^{k_{el}/(k_{el}-k_a)}$$

[i] Time of peak height:

$$\text{Day 1} = \ln\left(\frac{k_a}{k_{el}}\right)\Big/(k_a - k_{el}) + t_0$$

$$\text{Day 8} = \ln\left[\frac{k_a(1-e^{-k_{el}\tau})}{k_{el}(1-e^{-k_a\tau})}\right]\Big/(k_a - k_{el})$$

Table II—Pharmacokinetic Parameters of Theophylline after Single Intravenous Doses of Aminophylline Alone or during Steady State of Caffeine

Parameter	Dog A			Dog B		
	Aminophylline	Aminophylline + Caffeine		Aminophylline[b]	Aminophylline + Caffeine	
		Corrected[a]	Uncorrected		Corrected	Uncorrected[b]
k_{el}, hr^{-1}	0.098	0.11	0.05	—[c]	0.17	—
$t_{1/2}$, hr	7.10	6.08	13.7	—	4.03	—
D/V, μg/ml	9.96	9.96	17.5	—	8.56	—
V, liter/kg	0.75	0.75	0.43	—	0.85	—
r^2[d]	0.99	0.97	0.96	—	0.99	—
k_{12}, hr^{-1}	—	—	—	3.62	—	8.17
				(0.80–6.44)		(−23.4–39.7)
k_{21}, hr^{-1}	—	—	—	5.20	—	9.97
				(3.05–7.35)		(2.17–17.8)
k_{el}, hr^{-1}	—	—	—	0.24	—	0.16
				(0.19–0.29)		(−0.067–0.38)
α, hr^{-1}	—	—	—	8.92	—	18.2
$t_{1/2,\alpha}$[e], hr	—	—	—	0.078	—	0.038
β, hr^{-1}	—	—	—	0.14	—	0.086
$t_{1/2,\beta}$[f], hr	—	—	—	4.94	—	8.10
D/V_1, μg/ml	—	—	—	16.5	—	24.2
				(13.5–19.6)		(−10.2–58.6)
V_1, liter/kg	—	—	—	0.44	—	0.30
V_{ss}[g], liter/kg	—	—	—	0.74	—	0.55
R^2	—	—	—	1.00	—	1.00
Cl_p[h], ml/min/kg	1.22	1.42	0.36	1.76	2.43	0.78
$AUC^{0\to\infty}$[i], (μg hr)/ml	102	90.5	350	68.8	50.4	151

[a] Calculated using observed plasma theophylline concentration minus the theophylline formed as metabolite of caffeine. [b] Obtained by analyses using two-compartment model. [c] Not relevant. [d] Correlation coefficient. [e] Half-life of rapid phase of decline in plasma levels = $0.693/\alpha$. [f] $0.693/\beta$. [g] $V_{ss} = V_1(1 + k_{12}/k_{21})$. [h] Plasma clearance = Vk_{el} in one-compartment model and V_1k_{el} in two-compartment model. [i] Area under plasma level–time curve = D/Cl_p.

Complete peak resolution was obtained for caffeine, theophylline, and the internal standard, β-hydroxyethyltheophylline, with retention times of 9.6, 5.6, and 6.5 min, respectively. Other xanthines did not interfere. The limit of detection was 1 μg/ml for both theophylline and caffeine. Linear regressions of the peak height ratios of drug to internal standard *versus* plasma drug levels of 1, 5, 10, 25, and 50 μg/ml were described by the equations $y = 0.066x + 0.013$ ($n = 20, r = 1.00$) for theophylline and $y = 0.036x + 0.016$ ($n = 20, r = 1.00$) for caffeine.

Pharmacokinetic Analysis—Plasma caffeine levels after oral doses were fitted to the pharmacokinetic one-compartment open model with first-order absorption and elimination. Plasma caffeine concentrations, C, at any time, t, after a single dose are described by:

$$C = \frac{FD}{V}\left(\frac{k_a}{k_a - k_{el}}\right)[e^{-k_{el}(t-t_0)} - e^{-k_a(t-t_0)}] \qquad \text{(Eq. 1)}$$

where F is the fraction of the dose, D, absorbed; V is the apparent distribution volume of caffeine in the body; k_a and k_{el} are first-order rate constants for absorption and elimination, respectively; and t_0 is the lag time between dosing and the appearance of drug in the circulation. During steady state following multiple dosing, plasma caffeine concentrations, C^∞, were fitted to (12):

$$C^\infty = \frac{FD}{V}\left(\frac{k_a}{k_a - k_{el}}\right)\left(\frac{e^{-k_{el}t}}{1-e^{-k_{el}\tau}} - \frac{e^{-k_at}}{1-e^{-k_a\tau}}\right) \qquad \text{(Eq. 2)}$$

where τ is the dosing interval and equals 12 hr in each case.

Except in two cases, plasma theophylline levels after rapid intravenous doses of aminophylline appeared to obey one-compartment open model kinetics and were analyzed by linear regression (13). Attempts to fit these data to the two-compartment model resulted in greater errors in parameter values with no improvement in the coefficients of determination. In the two situations where the two-compartment model was adequate, plasma theophylline concentrations, C_1, were described by (12):

$$C_1 = \frac{D}{V_1(\alpha - \beta)}[(\alpha - k_{21})e^{-\alpha t} + (k_{21} - \beta)e^{-\beta t}] \qquad \text{(Eq. 3)}$$

where V_1 is the volume of the central compartment and α and β are composite rate constants depending on k_{el} and the first-order rate constants, k_{12} and k_{21}, governing the transfer of drug between compartments:

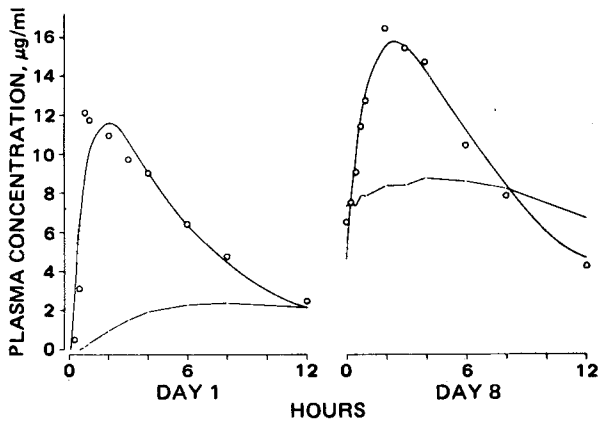

Figure 1—*Plasma levels of caffeine (○) and theophylline (– –) in Dog A after the morning dose on Days 1 and 8 during a 100-mg caffeine twice daily regimen. The curves for caffeine are computer derived.*

$$\begin{matrix}\alpha \\ \beta\end{matrix} = \tfrac{1}{2}\{(k_{12} + k_{21} + k_{el}) \pm [(k_{12} + k_{21} + k_{el})^2 - 4k_{21}k_{el}]^{1/2}\} \quad \text{(Eq. 4)}$$

Individual data sets were fitted to the appropriate equations by iterative least-squares methods using the program NONLIN[7] (14).

Pharmacokinetic parameters obtained from single-dose (Day 1) caffeine data were used to predict drug accumulation characteristics upon multiple dosing. Predicted parameter values were compared with those observed in the Day 8 experiment.

RESULTS

Plasma concentration–time data after single and multiple oral doses of caffeine to Dogs A and B are presented in Figs. 1 and 2, respectively. Results of pharmacokinetic analyses are given in Table I. Following single 100-mg tablet doses, caffeine appeared in plasma almost immediately, reaching peak levels of 11.6 and 9.97 μg/ml in 1–2 hr. Elimination half-lives were 3.84 hr in Dog A and 5.16 hr in Dog B. Accordingly, steady-state concentrations should be achieved in 1 day, and this projection was confirmed by the caffeine levels observed in the daily predose plasma samples.

Upon multiple dosing, caffeine absorption was slower in both dogs, as reflected by the prolonged absorption half-times and delayed peak times. The half-life was increased slightly after repeated dosing in Dog A but was decreased in Dog B. The value of FD/V was higher on Day 8 in each case. The area under the curve increased significantly in Dog A, but the change in Dog B was slight. The accumulation factor, R, calculated by the ratio of C_{max} on Day 8 to that on Day 1, was 1.34 for Dog A and 1.20 for Dog B; R values predicted from Day 1 data alone, using $R = 1/[(1 - e^{-k_{el}\tau})(1 - e^{-k_a\tau})]$, were 1.13 and 1.25 for Dogs A and B, respectively.

In humans, caffeine is metabolized in part by N-demethylation to theophylline (15). This route was shown to exist in dogs also in the present study. After a single 100-mg oral dose of caffeine, detectable plasma theophylline levels appeared in 45 min, reaching a plateau of ~2 μg/ml at 4 hr. The sustained nature of plasma theophylline in this case precluded the accurate calculation of its elimination rate. The accumulation factors obtained by the ratio of observed values of C_{max} on Day 8 and Day 1 were 3.67 and 2.66 for Dogs A and B, respectively.

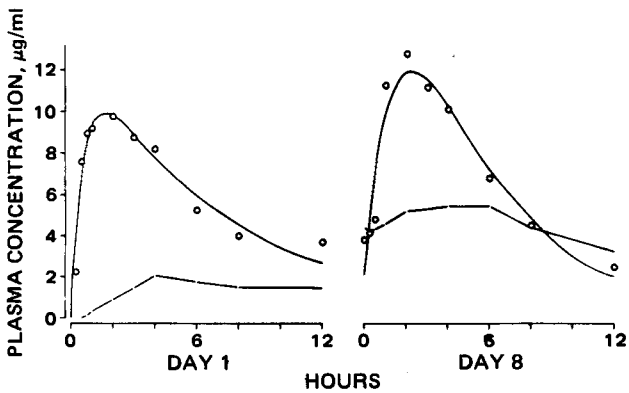

Figure 2—*Plasma levels of caffeine (○) and theophylline (– –) in Dog B after the morning dose on Days 1 and 8 during a 100-mg caffeine twice daily regimen.*

[7] An IBM 370/168 digital computer at the Rutgers Computer Center for Informational Services was used.

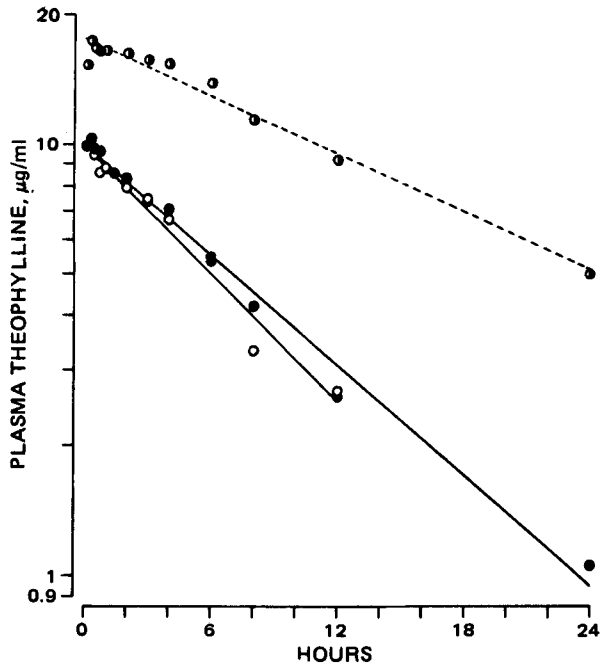

Figure 3—*Plasma theophylline levels in Dog A after 100 mg of aminophylline was intravenously administered alone (●) or during steady state of caffeine, with data corrected (○) and uncorrected (◑) for theophylline derived from caffeine, respectively.*

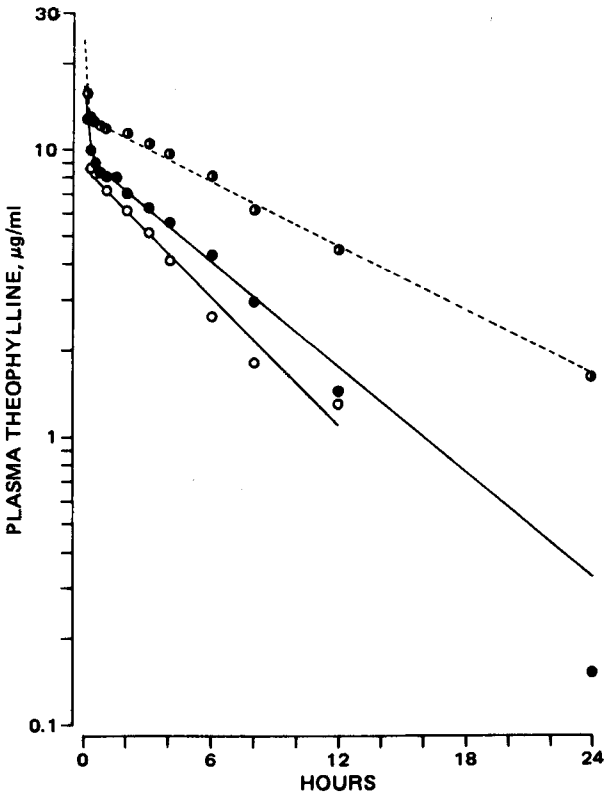

Figure 4—*Plasma theophylline levels in Dog B after 100 mg of aminophylline was intravenously administered alone (●) or during steady state of caffeine, with data corrected (○) and uncorrected (◑) for theophylline derived from caffeine, respectively.*

Table III—Pharmacokinetic Parameters of Caffeine after an Oral Dose during Steady State with Concomitant Aminophylline Injection

Parameter	Dog A	Dog B
k_a, hr^{-1}	1.67 (1.30–2.05)	8.82 (6.97–10.7)
$t_{1/2,abs}$, hr	0.41	0.079
k_{el}, hr^{-1}	0.12 (0.10–0.13)	0.14 (0.13–0.16)
$t_{1/2}$, hr	5.95	4.89
FD/V, μg/ml	13.7 (11.9–15.6)	11.1 (10.3–11.9)
r^2	0.98	0.99
$AUC^{0\to12}$, (μg hr)/ml	116	77.5
C_{max}, μg/ml	15.0	12.8
t_{max}, hr	1.52	0.45

Figures 3 and 4 describe plasma theophylline concentrations following bolus intravenous injections of 100 mg of aminophylline to Dogs A and B, respectively. While theophylline kinetics were being examined after simultaneous administration with the final dose of caffeine in the multiple caffeine dosing experiment, it was realized that caffeine metabolism resulted in sufficiently high theophylline levels to interfere with interpretation of data from the intravenous dose. Therefore, corrected plasma theophylline levels from the aminophylline injection (Day 9) were estimated by deducting from observed values the theophylline concentrations at the same sampling time on the previous day (Day 8). This procedure was justified by the observed theophylline concentrations in the daily predose plasma samples, which showed that this metabolite also had reached steady state. Both corrected and uncorrected theophylline data were analyzed, and the results of the pharmacokinetic analyses are shown in Table II.

Except for a short initial period (15 min) of rapid decline in plasma levels in two cases, theophylline pharmacokinetics were described adequately by the one-compartment open model. Despite its higher initial concentration in Dog B (16.5 μg/ml, compared to 9.96 μg/ml in Dog A), theophylline appeared to distribute into virtually identical overall spaces in Dogs A (V = 0.75 liter/kg) and B (V_{ss} = 0.74 liter/kg). Elimination half-lives of 7 and 5 hr were observed in Dogs A and B, respectively.

Pharmacokinetic analysis of corrected theophylline data showed that a concomitant dose of aminophylline with caffeine at steady state of caffeine resulted in little or no change in the apparent distribution volume of theophylline in the two dogs. However, the half-life was shortened by ~1 hr in each dog. The increase in the elimination rate was reflected also in changes in the plasma clearance and area under the curve values. As expected, analysis of the uncorrected data led to much higher initial plasma theophylline concentrations (17.5 μg/ml in Dog A and 24.2 μg/ml in Dog B) and longer half-lives (13.7 and 8.10 hr in Dogs A and B, respectively).

Pharmacokinetic parameters of caffeine after concomitant caffeine and aminophylline doses on Day 9 are given in Table III. Comparison with the Day 8 data in Table I indicated that the injection of aminophylline resulted in faster absorption of caffeine from the oral dose (larger k_a and smaller t_{max} in both dogs), although C_{max} values were almost unchanged. These results also are shown in Figs. 5 and 6 for Dogs A and B, respectively. Aminophylline increased the elimination half-life of caffeine but decreased the FD/V values so that the area under the plasma caffeine level–time curve during a dose interval was virtually unaffected.

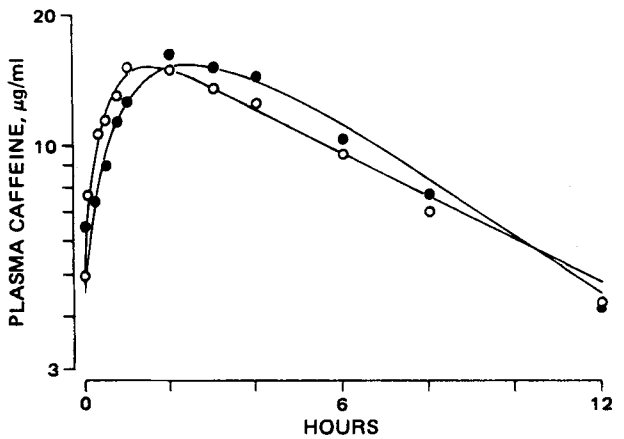

Figure 5—*Steady-state plasma caffeine levels in Dog A after oral administration of 100 mg of caffeine, with (○) and without (●) a concomitant dose of intravenous aminophylline.*

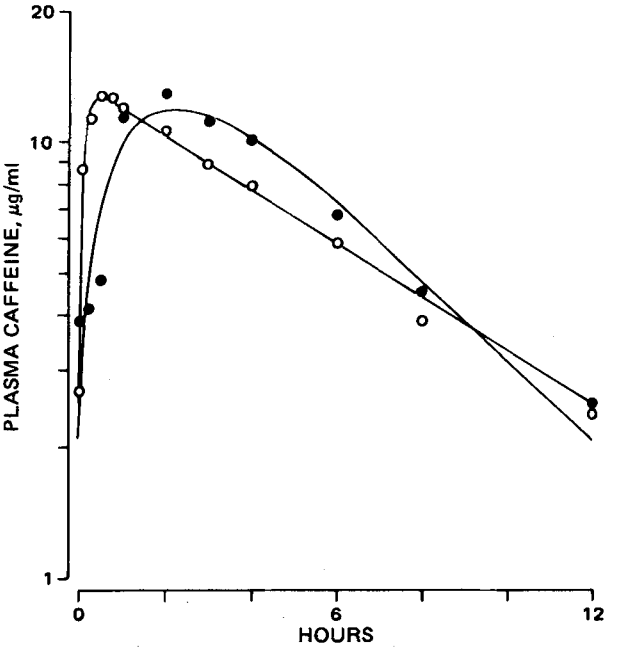

Figure 6—*Steady-state plasma caffeine levels in Dog B after oral administration of 100 mg of caffeine, with (○) and without (●) a concomitant dose of intravenous aminophylline.*

DISCUSSION

The caffeine half-life determined after single oral doses to dogs was 4–5 hr, similar to that observed in humans (15). However, longer half-life values (6.4–9.1 hr) were reported in a more recent study in three healthy nonsmokers (16). Intersubject variation in caffeine kinetics was apparent in the present study. This variation and the limited number of dogs used made it difficult to evaluate the effect of repeated dosing on caffeine pharmacokinetic properties. With the dosage regimen employed, which was equivalent to about 1 cup of coffee every 12 hr, there was limited accumulation of caffeine in the circulation. On the other hand, plasma levels of the N-demethylated metabolite, theophylline, rose to nearly 9 and 6 μg/ml in Dogs A and B, respectively, about three times the concentrations after the initial dose. These figures were higher than those reported in humans given comparable doses of caffeine (15). Therefore, subjects must refrain from caffeine-containing beverages before participating in theophylline disposition studies, despite recent advancements in analytical technology that permit simultaneous determination of caffeine and theophylline in biological fluids.

The decline in plasma theophylline levels after intravenous dosing appeared to be biphasic, although the distribution phase was so rapid that a one-compartment model was adequate for data analysis in four of the six cases tested. This characteristic behavior was reported by others (6, 17). The theophylline half-life in dogs after single doses was similar to that in humans. When given concomitantly with caffeine during steady state of caffeine, theophylline showed slight increases in its elimination rate, probably due to metabolic enzyme activity stimulated by the repeated caffeine doses. The distribution volume (0.75 liter/kg) of theophylline was unaltered by caffeine.

No explanation was apparent for the more rapid absorption of caffeine when given simultaneously with intravenous aminophylline. Starr *et al.* (18) reported that aminophylline increased cardiac output in humans by 26% and also may enhance blood flow through the GI tract. Further studies are being conducted to elucidate this phenomenon. Aminophylline prolonged the elimination half-life of caffeine, presumably by competing with caffeine for the same enzymes. Aminophylline also increased the apparent distribution volume of caffeine (assuming constant F), probably by displacing caffeine from plasma protein binding sites. Thus, theophylline appeared to have a stronger affinity than caffeine for drug metabolizing enzymes as well as for plasma proteins. In humans, theophylline is 60–70% plasma protein bound (19, 20), compared to ~15% in the case of caffeine (21). Because of changes in V and k_{el} in opposite di-

rections, the overall plasma clearance of caffeine was virtually unaffected by acute aminophylline administration.

The need for establishing dosage guidelines for safe intravenous administration of theophylline has been stressed (22). Theophylline has a narrow therapeutic index of 10–20 μg/ml, and the risk of toxicity, including seizures and death, increases as serum concentrations exceed this range. In asthmatic patients receiving chronic theophylline therapy, routine monitoring of serum drug levels is recommended. Interactions of theophylline with other exogenous compounds may influence the therapeutic outcome of this drug. For example, methylxanthines such as caffeine and theobromine, present in various common beverages and foods, were shown to inhibit theophylline metabolism in humans (9). In the present study, the theophylline half-life in beagle dogs actually decreased after multiple doses of caffeine, probably due to enzyme induction by the latter. Nevertheless, plasma theophylline levels were elevated and sustained as a result of metabolic conversion of administered caffeine to theophylline.

These observations may suggest the need to reduce theophylline maintenance doses in asthmatics who are chronic coffee drinkers. Caution is also warranted in treatment with theophylline in breast-fed infants, who may be exposed to methylxanthines in the milk (23, 24). Recently it has become evident that theophylline is biotransformed to caffeine by *N*-methylation in the premature newborn infant (25–28), which further complicates theophylline–caffeine interactions. This metabolic pathway was not observed in adult humans (25) and dogs in the present study.

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Nonsteroidal Estrogens and Antiestrogens: Biological Activity of Cyclopropyl Analogs of Stilbene and Stilbenediol

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Abstract □ The estrogenic, antiestrogenic, and receptor binding activity of a series of cyclopropyl analogs of stilbene and stilbenediol were determined using the uterotropic assay in the mouse and the receptor binding assay with rat uterine cytosol. One compound, 1,1-dichloro-*cis*-2,3-diphenylcyclopropane (II), displayed antiestrogenic activity *in vivo* with a low affinity for the estrogen receptor *in vitro* and showed tumor remission activity on 7,12-dimethylbenz(*a*)anthracene-induced estrogen-dependent rat mammary tumors. Compounds VIII, IV, and V (in that order) exhibited the greatest estrogenic activity in the mouse and the greatest receptor binding activity *in vitro*. Compound VIII exhibited antifertility activity in the mouse.

Keyphrases □ Estrogenic activity—cyclopropyl analogs of stilbene and stilbenediol, mice □ Antiestrogenic activity—cyclopropyl analogs of stilbene and stilbenediol, mice □ Receptor binding activity—cyclopropyl analogs of stilbene and stilbenediol □ Stilbene and stilbenediol—cyclopropyl analogs, pharmacological activity in mice and rats

Various rigid ring systems have been used to lock functional groups into desired conformations to study receptor interactions (1, 2). The cyclopropane ring is a relatively new structure to be employed synthetically to produce a fixed stereochemical configuration with minimal steric interference in potential medicinal agents (3–5). Magarian and Benjamin (6) reported the preparation of a series of stilbene and stilbenediol derivatives (Table I) containing