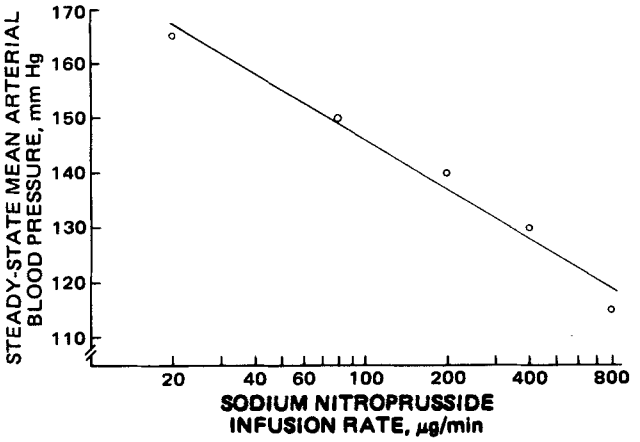

Figure 1—*Relationship between steady-state mean arterial blood pressure and sodium nitroprusside infusion rate in one patient with malignant hypertension. The linear regression line is shown (r = −0.99).*

representative patients. Data on one patient, a 45-year-old male with malignant hypertension, renal failure, and congestive heart failure, were presented in sufficient detail to permit the proposed analysis. In accordance with Eq. 4*b*, a linear relationship was obtained between steady-state mean arterial blood pressure and the logarithm of sodium nitroprusside infusion rate over a 40-fold range of zero-order infusion rates (Fig. 1). As shown in Fig. 2, plotting the time course of the hypotensive effect declining from steady state following discontinuation of sodium nitroprusside infusion illustrates adherence to Eq. 7*b*.

Calculation of the slopes in Figs. 1 and 2 provides direct estimates of m and mK of −30.1 mm Hg and 1.40 mm Hg/min, respectively. Therefore, K can be estimated as 0.0465 min^{-1} with a corresponding biological half-life of 14.9 min. This estimate of biological half-life is consistent with the rapidly achieved steady-state hypotensive response observed clinically. This relatively short half-life supports the prior interpretation of the mean arterial blood pressures in Fig. 1 as being reasonable approximations of steady-state values.

This analysis for sodium nitroprusside is exemplary of the potential utility of studying the pharmacokinetic properties of intravenously administered drugs eliciting a quantifiable response. Constant-rate intravenous infusion of a drug having a relatively short biological half-life will enable rapid achievement of steady state at each of the several infusion rates. Although this technique may not be applicable to all drugs, it may provide a basis for practical, exploratory analysis of pharmacological effect data for drugs such as nitroprusside, diazoxide, nitroglycerin, and trimethaphan.

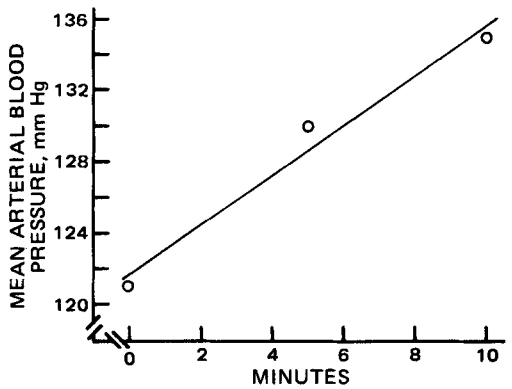

Figure 2—*Time course of increasing mean arterial blood pressure following discontinuation of sodium nitroprusside infusion. The linear regression line is shown (r = 0.99).*

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Plasma Theobromine after Oral Administration of Caffeine to Dogs

Keyphrases □ Theobromine—caffeine metabolite, plasma levels following oral administration of caffeine to dogs □ Caffeine—metabolism in dogs, plasma theobromine levels following oral administration of caffeine to dogs □ Metabolism—of caffeine, plasma levels of metabolite theobromine following oral administration of caffeine to dogs

To the Editor:

Caffeine (1,3,7-trimethylxanthine), a compound in coffee, tea, and many other beverages, has been used successfully for the treatment of apnea in premature infants

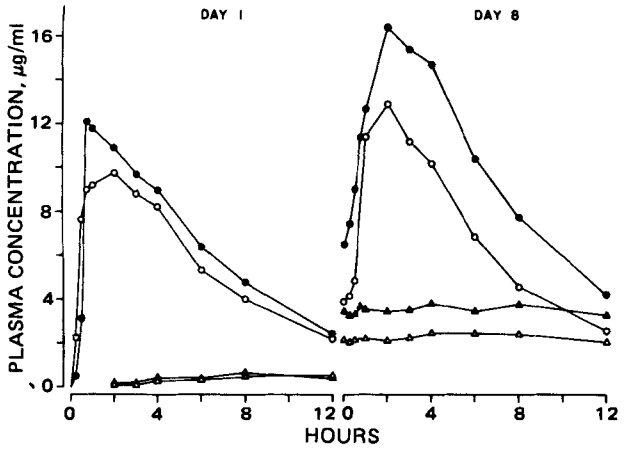

Figure 1—*Plasma concentrations of caffeine (●, Dog A; and ○, Dog B) and theobromine (▲, Dog A; and △, Dog B) after the morning doses on Days 1 and 8 during a 100-mg caffeine twice daily regimen.*

(1). Caffeine is absorbed efficiently following oral doses in humans and is eliminated almost entirely by biotransformation (2).

A first step in caffeine metabolism in humans is *N*-demethylation, which may occur at the 1-, 3-, or 7-position. It was suggested that the removals of the 3- and 7-methyl groups to form 1,7-dimethylxanthine and theophylline, respectively, are the major pathways, while the removal of the 1-methyl group to form theobromine is of minor importance (3). Nevertheless, 5% of an administered dose of caffeine was excreted as theobromine in rats (4). Another investigation found the same pathway in beagle dogs after single intravenous caffeine doses of 20 mg/kg (5).

In a recent study in this laboratory (6), the pharmacokinetics of caffeine were examined after single and repeated oral doses to beagle dogs. Theobromine was detected as a metabolite in plasma. Significant accumulation of this metabolite was observed after multiple caffeine doses, as described here.

Two beagle dogs (1-year-old male, Dog A, 11.4 kg, and 2-year-old female, Dog B, 11.7 kg) each received one 100-mg caffeine tablet[1] twice daily at 9:00 am and 9:00 pm for 8 days. The dogs were fasted overnight before the morning doses on Days 1 and 8, after which serial venous blood samples were collected. Plasma caffeine and theobromine were measured by high-performance liquid chromatography as previously described (6). Complete peak resolution was obtained for caffeine, theobromine, and β-hydroxyethyltheophylline (the internal standard), with retention times of 9.6, 4.0, and 6.5 min, respectively. Other xanthines did not interfere.

[1] NoDoz, Bristol-Myers, New York, N.Y.

Individual plasma caffeine and theobromine concentrations in the two dogs are summarized in Fig. 1. Caffeine was absorbed efficiently from a single oral dose, reaching the peak plasma level at 1–2 hr. The average elimination half-life calculated by nonlinear regression analysis (7) of individual data was 4.5 hr. Detectable theobromine levels appeared in the plasma at 2 hr following caffeine administration, rising slowly to 0.5–0.6 μg/ml at 8 hr. The peak time and normalized peak concentration showed excellent agreement with an earlier report (5). After repeated doses of caffeine, the drug showed some accumulation as predicted from the single-dose data. The average caffeine half-life was 3.9 hr, slightly shorter than the single-dose case. Of primary interest here, however, was the accumulation of the metabolite, theobromine. The Day 8 plasma levels, apparently at steady state, indicated a five- to six-fold increase from the single-dose data.

Results of the present study provided quantitative information on *N*-demethylation of caffeine in the dog to form theobromine. While plasma theobromine levels after a single caffeine dose were low, significant accumulation of this metabolite occurred after repeated caffeine administration. This phenomenon needs to be verified in humans. Since theobromine shares some of the common pharmacological activities of caffeine and theophylline (8), it may be necessary to recognize circulating levels of this metabolite when monitoring patients on caffeine therapy.

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