# Dose-Dependent Pharmacokinetics and Psychomotor Effects of Caffeine in Humans

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*Twelve healthy volunteers received oral placebo, 250 mg of caffeine, and 500 mg of caffeine in a randomized, double-blind, single-dose crossover study. Caffeine kinetics were nonlinear, with clearance significantly reduced and elimination half-life prolonged at the 500-mg compared to the 250-mg dose. The lower dose of caffeine produced more favorable subjective effects than the higher dose (elation, peacefulness, pleasantness), whereas unpleasant effects (tension, nervousness, anxiety, excitement, irritability, nausea, palpitations, restlessness) following the 500-mg dose exceeded those of the 250-mg dose. The lower dose of caffeine enhanced performance on the digit symbol substitution test and a tapping speed test compared to placebo; high-dose caffeine produced less performance enhancement than the lower dose. The plasma concentration versus response relationship revealed concentration-dependent increases in anxiety and improvements in cognitive and motor performance at low to intermediate concentrations. Both caffeine doses reduced electroencephalographic amplitude over the 4 Hz to 30 Hz spectrum, as well as in the alpha (8–11 Hz) and beta (12–30 Hz) ranges; however, effects were not dose-dependent. While favorable subjective and performance-enhancing stimulant effects occur at low to intermediate caffeine doses, the unfavorable subjective and somatic effects, as well as performance disruption, from high doses of caffeine may intrinsically limit the doses of caffeine used in the general population.*

Caffeine is a widely consumed psychoactive substance found in a variety of beverages, foods, and medicines.[1,2] The stimulant effects of caffeine on mood, attention, and performance are widely recognized.[3–6] Like other drugs of abuse, caffeine has psychoactive and reinforcing effects, its use often becomes habitual, and tolerance and discontinuation syndromes may result with repeated exposure.[7–9] Unlike other drugs of abuse, its stimulant, discriminative, and reinforcing effects are weak (e.g., compared to amphetamines), and its use usually does not become compulsive.[10] Caffeine and its methylxanthine metabolites mediate their effects by binding to adenosine receptors and antagonizing the effects of endogenous adenosine with the following potency profile: theophylline > caffeine > theobromine.[11] The behavioral stimulant potencies of methylxanthines correlate with their affinity for adenosine receptors.[12] *In vivo* caffeine treatment stimulates behavioral activity as it occupies adenosine $A_1$ subtype receptors.[13]

Caffeine is well known for its psychoactive effects, including stimulation of mood and psychomotor performance.[3–6,14–19] Dose-dependent effects of single doses of caffeine have been found in animal models and in human subjects, with positive stimulant effects at low and intermediate doses and more aversive effects at high doses. The maximal stimulatory effects of caffeine on activity in rodents are found at low to intermediate doses and intermediate plasma and brain caffeine concentrations (10–20 μg/mL or μg/g, respec-

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**TABLE I**

**Subject Characteristics**

| Subject No. | Age (yr) | Gender | Weight (kg) | Smoking (cigarettes/day) | No. of Caffeine-Containing Beverages per Day |
|---|---|---|---|---|---|
| 1 | 25 | M | 56.8 | 10 | 2 |
| 2 | 36 | F | 68.2 | 0 | 1 |
| 3 | 38 | M | 72.7 | 0 | 1.5 |
| 4 | 26 | F | 60.0 | 0 | 4 |
| 5 | 25 | F | 66.4 | 0 | 5 |
| 6 | 25 | F | 56.4 | 0 | 1 |
| 7 | 35 | M | 81.8 | 20 | 3 |
| 8 | 22 | F | 54.5 | 0 | 0 |
| 9 | 41 | F | 72.7 | 0 | 7 |
| 10 | 25 | F | 54.5 | 0 | 0 |
| 11 | 25 | M | 71.4 | 0 | 4 |
| 12 | 23 | M | 86.4 | 0 | 2 |

*M, male; F, female.*

tively).[20,21] Similarly, the rewarding effects of caffeine were demonstrated at low doses (3 mg/kg) in rats as shown by place preferences for environmental stimuli associated with the drug.[22] In this study, high-dose caffeine (30 mg/kg) produced aversive effects as demonstrated by significant place aversions.

In humans, low to intermediate doses of caffeine (generally <500 mg) also have stimulant and euphoric effects and increase arousal, alertness, concentration, sense of well-being, and performance on cognitive and motor tasks. High doses (>500 mg) cause nervousness and adverse somatic effects such as restlessness, agitation, chills, tremors, nausea, and diuresis, and disrupt performance.[10,14–19] High doses of caffeine (10 mg/kg) have been shown to provoke aversive anxiogenic effects in both normal subjects[23,24] and induce even greater effects in individuals with panic disorder.[25] Similarly, moderate (250 mg) and high (500 mg) caffeine doses provoked greater anxiety in patients with generalized anxiety disorder than in normal volunteers.[26]

Subjective effects of caffeine have correlated with quantitative pharmacodynamic measures, such as the electroencephalogram (EEG).[16–19,27,28] In normal volunteers, single doses of caffeine at 250 mg and 500 mg produced reductions in theta, alpha, and beta ampli-

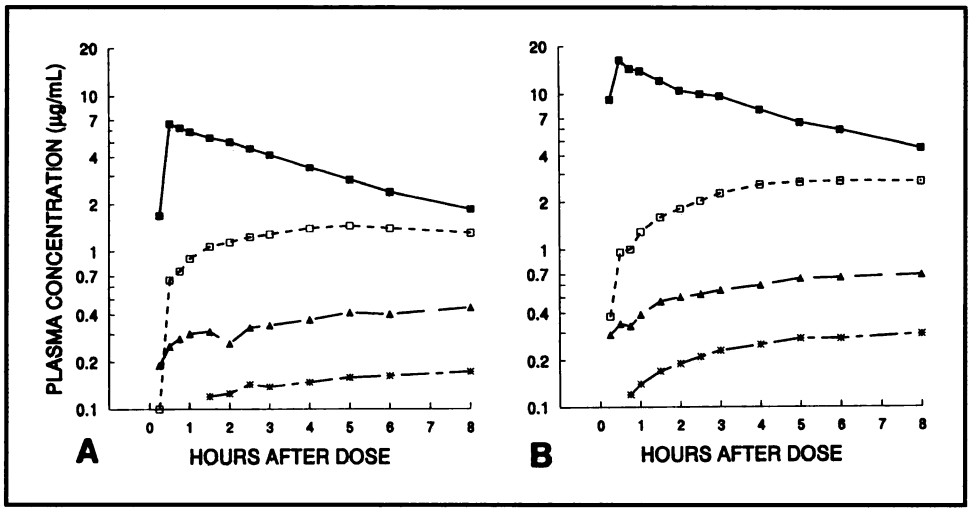


*Figure 1. Mean plasma concentrations of caffeine, paraxanthine, theobromine, and theophylline following single oral doses of 250 mg (A) or 500 mg (B) of caffeine. Each point is the mean value for all subjects at the corresponding time. ■, caffeine; □, paraxanthine; ▲, theobromine; *, theophylline.*

**TABLE II**

**Effect of Dose on Kinetic Variables for Caffeine and Metabolites**

| | Mean (±SE) Value | | |
|---|---|---|---|
| | 250 mg Caffeine | 500 mg Caffeine | Value of Student's t Test |
| Caffeine | | | |
| $C_{max}$ (μg/mL) | 7.0 (±0.5) | 17.3 (±1.4) | 2.13 ($P < 0.06$)* |
| $t_{max}$ (hr after dose) | 0.65 (±0.09) | 0.50 (±0.06) | 1.47 (NS) |
| $t_{1/2}$ (hr) | 3.94 (±0.5) | 4.74 (±0.6) | 2.37 ($P < 0.05$) |
| Vd | | | |
| L | 38.8 (3.6) | 35.8 (±2.7) | 1.88 (NS) |
| L/kg | 0.58 (±0.03) | 0.53 (±0.03) | 1.95 (NS) |
| Clearance | | | |
| mL/min | 142 (±29) | 113 (±24) | 3.49 ($P < 0.01$) |
| mL/min/kg | 2.07 (±0.4) | 1.64 (±0.3) | 3.77 ($P < 0.005$) |
| Paraxanthine | | | |
| 8-hour AUC (μg/mL · hr) | 9.43 (±0.42) | 17.3 (±0.93) | 1.54 (NS)* |
| Theobromine | | | |
| 8-hour AUC (μg/mL · hr) | 2.78 (±0.55) | 4.29 (±0.90) | 2.24 ($P < 0.05$)* |
| Theophylline | | | |
| 8-hour AUC (μg/mL · hr) | 1.00 (±0.10) | 1.67 (±0.18) | 1.44 (NS)* |

* *Student's t test performed after normalization for dosage.*

*$C_{max}$, peak plasma concentration; $t_{max}$, time to reach $C_{max}$; $t_{1/2}$, elimination half-life; Vd, apparent volume of distribution; AUC, area under the concentration–time curve; NS, not significant.*

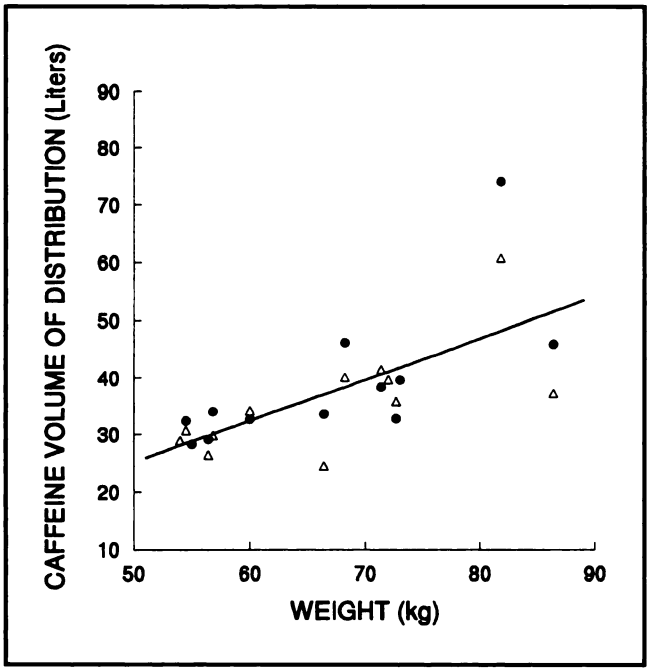


*Figure 2. Relation of body weight to caffeine volume of distribution. ●, 250 mg of caffeine; △, 500 mg of caffeine.*

tudes and in total power as they produced subjective effects of increased alertness, energy, quick-wittedness, and attentiveness.[16] Interestingly, other studies showed heterogeneous caffeine dose–response relationships using various psychomotor measures including EEG.[19] A single dose of theophylline (400 mg) produced reductions in theta, alpha, beta, and total amplitudes, but this was not associated with any mood effects.[28] These last two studies suggest that methylxanthine-induced quantitative EEG effects are variable in their correlation with subjective effects.

The present study examines the pharmacokinetic and pharmacodynamic effects of a moderate dose (250 mg) and a high dose (500 mg) of caffeine in normal volunteers. This study extends previous caffeine research by more extensively quantifying dose-dependent kinetics and psychomotor effects. Specifically, this study examines if the pharmacokinetics and the subjective, cognitive, and motor effects of single-dose caffeine treatment are dose- and/or concentration-dependent.

## METHODS

The protocol was reviewed and approved by the Human Investigation Review Committee of Tufts University School of Medicine and New England Medi-

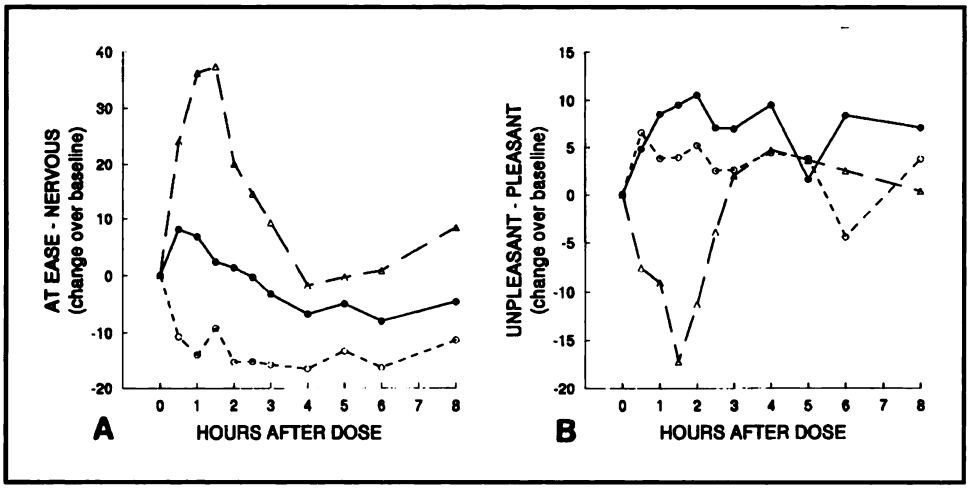


*Figure 3. Effect of placebo (○- -○), 250 mg of caffeine (●–●), and 500 mg (△– –△) of caffeine on self-ratings of two items from the series of 100-mm visual analog scales (A, at ease–nervous; B, unpleasant–pleasant). Postdosage scores represent the increment or decrement over the predose baseline rating. Each point is the mean value for all subjects at the corresponding time.*

cal Center Hospital (Boston, MA). Twelve healthy male and female volunteers, 20 to 46 years old, participated after giving written informed consent (Table I). All were active ambulatory adults with no evidence of medical disease and taking no other medications. Two of the subjects were cigarette smokers. Ten of the participants were regular users of caffeine in the form of coffee or other caffeine-

**TABLE III**

**Influence of Caffeine and Placebo on 4-Hour Effect Area Measures from Visual Analog Scales***

| Scale Item† | Mean 4-Hour Effect Area | | | F Value (repeated-measures analysis of variance)‡ |
|---|---|---|---|---|
| | Placebo | 250 mg Caffeine | 500 mg Caffeine | |
| Sedation (self-rated) | −18.9 | 23.7 | −15.9 | 0.13 (NS) |
| Sedation (observer-rated) | 1.63 | 1.3 | 0.3 | 0.24 (NS) |
| Calm/anxious | −22.7 | 15.5 | 74.2 | 9.57 ($P < 0.001$) |
| Energetic/fatigued | −24.6 | −18.9 | −28.1 | 0.08 (NS) |
| Thinking slowed down/ thinking speeded up | 1.0 | 28.4 | 27.3 | 1.32 (NS) |
| Peaceful/tense | −22.9 | −0.1 | 64.8 | 5.17 ($P < 0.02$) |
| Normal/spacey | −9.0 | −20.4 | 6.4 | 2.38 (NS) |
| Friendly/seclusive | 0.8 | −16.0 | 5.1 | 2.41 (NS) |
| Normal/elated | −19.9 | 29.2 | 8.4 | 3.87 ($P < 0.05$) |
| Unhungry/hungry | 68.2 | 22.2 | 32.8 | 1.84 (NS) |
| Unpleasant/pleasant | 15.1 | 30.2 | −20.7 | 5.76 ($P < 0.01$) |
| At ease/nervous | −52.2 | 1.9 | 72.0 | 12.66 ($P < 0.001$) |
| Relaxed/excited | −33.8 | 24.4 | 83.0 | 12.71 ($P < 0.001$) |
| Normal/easily irritated | −12.1 | −4.6 | 25.8 | 3.78 ($P < 0.05$) |
| Discontented/contented | 24.4 | 15.8 | −1.8 | 1.03 (NS) |

* *Effect areas were calculated from change scores (vs. baseline) using the trapezoidal method.*

† *For sedation, higher numbers indicate higher sedation ratings. For other measures, the indicated terms (divided by slash mark) appear at extreme left and right of the scale, respectively. Positive numbers indicate ratings in the rightward direction.*

‡ *The Student-Newman-Keuls test evaluated differences among individual treatments. Values not underlined together are significantly different ($P < 0.05$). No underlines appear when overall analysis of variance was not significant, in which case no individual differences were significant.*

*NS, not significant.*

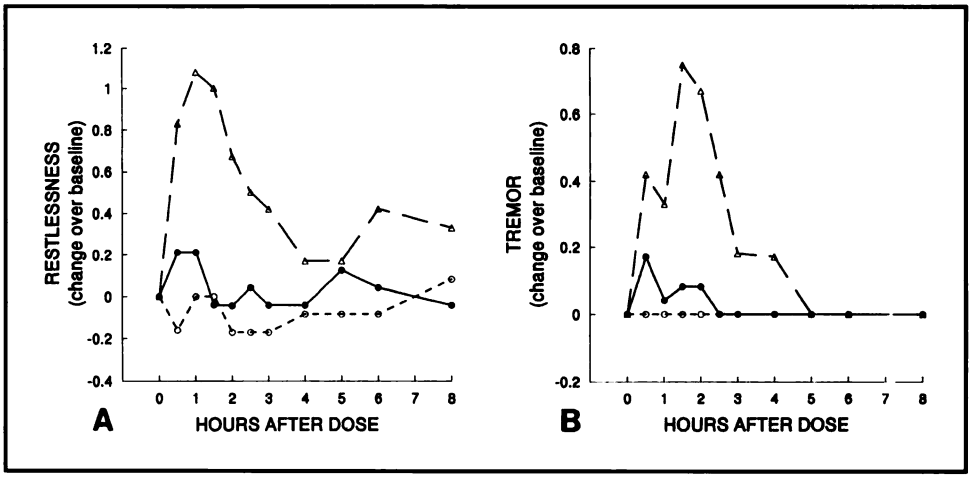


*Figure 4. Effect of placebo (○- -○), 250 mg of caffeine (●–●), and 500 mg (△– –△) of caffeine on self-ratings of two items from the somatic and autonomic symptom scale (A, restlessness; B, tremor). Postdosage scores represent the increment or decrement over the predose baseline rating. Each point is the mean value for all subjects at the corresponding time.*

containing beverages. They were asked to abstain from all caffeine for 24 hours prior to each study trial.

The study had a double-blind, single-dose, three-way crossover design. Medications were identically packaged in opaque capsules and administered orally, with at least 1 week elapsing between trials. The three treatment conditions were: 1) caffeine, 250 mg; 2) caffeine, 500 mg; and 3) placebo. These two caffeine doses span the range of what might be present in several "strong" caffeine-containing beverages, such as coffee, up to amounts that individuals may ingest in tablet or capsule form for purposes of producing and maintaining alertness or enhancing performance.[1,2]

Subjects entered the General Clinical Research Center of New England Medical Center Hospital on the morning of each trial. They ingested a light liquid breakfast, with no caffeine-containing beverages, approximately 90 minutes before medication. Subjects remained fasting until 3 hours after administration, after which they resumed a normal diet (without caffeine-containing beverages). The study medication was administered at 9:00 AM with 250 mL of tap water.

Venous blood samples were drawn from an indwelling cannula into heparinized tubes prior to dosage and at the following postdosage times: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, and 8 hours. Samples were centrifuged, and the plasma separated and frozen until the time of assay.

A five-electrode midline EEG montage was affixed as follows: frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz), with a nose electrode as reference. Procedures for preparation of electrode sites and affixing of electrodes are described previously.[29–30] The recording instrument was a Brain Electrical Activity Machine (BEAM; NeuroScience, Inc., Milpitas, CA). The EEG was recorded in 4-second epochs, for as long as necessary to ensure at least 2 minutes of artifact-free information, prior to and at 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, and 8 hours after dosage. The EEG tracings were reviewed by a blind observer so that only artifact-free segments were analyzed. Data were digitized over the power spectrum from 4 to 30 cycles per second (Hz), and analyzed by fast Fourier transform to determine amplitude in the total spectrum (4–30 Hz) and in the beta (12–30 Hz) and alpha (8–11 Hz) frequency ranges.

Subjects' self-ratings of sedative effects and mood state were obtained on a series of 100-mm visual analog scales.[29–31] Ratings of sedation were also performed by a trained observer, with the same rating instrument, without knowledge of the treatment condition. Self- and observer-ratings were obtained twice prior to medication administration and at postdosage time points corresponding to EEG recordings. Self-ratings of a number of somatic symptoms were obtained using a 16-item scale with discrete ratings (1 = none, 2 = mild, 3 = moderate, 4 = severe).

The digit symbol substitution test (DSST) was administered twice prior to dosing and at 0.5, 1, 2, 3, 4, 6, and 8 hours after dosage.[29–31] Subjects were asked to make as many correct symbol-for-digit substitutions as possible within a 2-minute period. For each DSST, subjects completed an arbitrarily selected equivalent test variant such that no individual took the same test more than once. A 60-second test of tapping speed was performed twice prior to dosage and at 1, 2, 4, 6, and 8 hours after dosage.[32] Subjects were trained in the DSST and tapping tests approximately 1 week before starting the drug trial.

**TABLE IV**

**Influence of Caffeine and Placebo on 4-Hour Effect Area Measures from Somatic Symptom Scales***

| Scale Item† | Mean 4-Hour Effect Area | | | F Value (repeated-measures analysis of variance)‡ |
|---|---|---|---|---|
| | Placebo | 250 mg Caffeine | 500 mg Caffeine | |
| Nausea | −0.50 | −0.43 | 0.50 | 6.68 ($P < 0.01$) |
| Perspiration | −0.23 | 1.27 | 1.97 | 5.65 ($P < 0.02$) |
| Palpitations | 0 | 0.15 | 0.93 | 5.30 ($P < 0.02$) |
| Paresthesias (tingling, numbness | 0.01 | −0.62 | 0.59 | 4.24 ($P < 0.03$) |
| Chest pain | 0 | 0 | 0.06 | 1.0 (NS) |
| Restlessness | −0.42 | 0.14 | 2.44 | 11.12 ($P < 0.001$) |
| Choking feeling | 0 | −0.20 | 0.04 | 1.22 (NS) |
| Anorexia (loss of appetite) | 0.10 | 0.20 | 0.81 | 1.13 (NS) |
| Dizziness | 0 | 0 | 0.17 | 3.14 ($P < 0.07$) |
| Faintness | 0 | −0.16 | 0.15 | 1.32 (NS) |
| Tremor | 0 | 0.19 | 1.60 | 8.26 ($P < 0.005$) |
| Hot and cold flashes | −0.50 | 0.04 | 0.17 | 2.30 (NS) |
| Unreal feelings | 0.04 | 0 | 0.31 | 1.36 (NS) |
| Weakness | −0.15 | 0.31 | 0.45 | 1.08 (NS) |
| Dyspnea (difficulty breathing) | 0 | 0 | 0.13 | 1.0 (NS) |
| Fear of losing control | 0 | 0 | 0.14 | 1.0 (NS) |
| Fear of going crazy | 0 | 0 | 0 | NS |
| Headache | 0.44 | −0.34 | −0.39 | 1.19 (NS) |

* *Effect areas were calculated from change scores (vs. baseline) using the trapezoidal method.*
† *Positive numbers indicate higher ratings.*
‡ *The Student-Newman-Keuls test evaluated differences among individual treatments. Values not underlined together are significantly different ($P < 0.05$). No underlines appear when overall analysis of variance was not significant, in which case no individual differences were significant.*
*NS, not significant.*

Plasma concentrations of caffeine and its principal metabolites (paraxanthine, theobromine, and theophylline) in each sample were determined by high-performance liquid chromatography.[20,33] Model-independent methods were used to determine the following kinetic parameters for caffeine: peak plasma

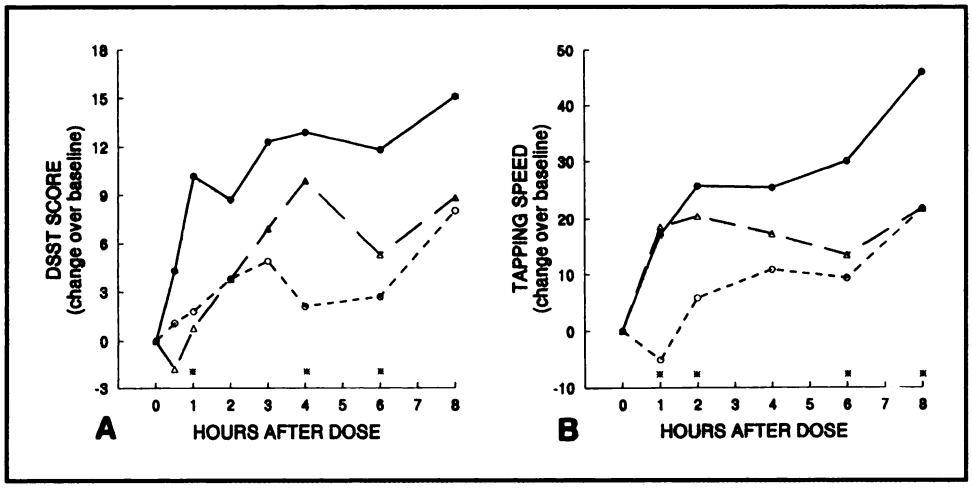


*Figure 5. Scores on the digit symbol substitution test (DSST) (A) and tapping speed test (B) (○- -○, placebo; ●–●, 250 mg of caffeine; △– –△, 500 mg of caffeine). Postdosage scores represent the increment or decrement over the predose baseline score. Each point is the mean value for all subjects at the corresponding time. Asterisks along the x axis indicate a significant difference among the three treatments at that time point.*

concentration ($C_{max}$), time of peak concentration ($t_{max}$), elimination half-life ($t_{1/2}$), apparent volume of distribution ($V_d$), and total clearance.[29–31] Also evaluated were area under the 8-hour plasma concentration curve for each of the metabolites. In some instances predose plasma levels of metabolites were nonzero, in which case measures of area under the curve were corrected for the value at time zero.

For self- and observer-ratings on visual analog scales and on the somatic symptom scale, the two predose baseline ratings were averaged, and all postdosage scores were expressed as the increment or decrement relative to the mean predose value. Scores on the DSST and tapping speed test were similarly analyzed.

For each 2-minute EEG recording, total amplitude, alpha amplitude, and beta amplitude in the predose recording was used as the baseline. All postdosage values were expressed as the increment or decrement over the predose baseline value. Electroencephalogram data were also evaluated as changes in fractional beta and fractional alpha range amplitude (relative to amplitude over the total 4–30 Hz range) at individual time points.

Area under the 4-hour plot of effect change score versus time was calculated for each pharmacodynamic variable. This is a standard pharmacodynamic procedure to measure effect size.[31] The effect area can be either positive or negative depending on the direction of the change.

Statistical procedures included linear regression, analysis of variance, the Student-Newman-Keuls multiple comparison procedure, and student's *t* test. Analysis of variance indicated no significant difference among the three treatment conditions in predose baseline values of any of the pharmacodynamic variables.

## RESULTS

Predose plasma caffeine concentrations were undetectable in 11 of the subjects and were less than 0.1 μg/mL in the others. However, baseline theobromine concentrations exceeding 0.3 μg/mL were measured in four subjects. These findings are consistent with the requirement of caffeine abstinence.[34]

Caffeine was rapidly absorbed from the oral capsule preparation, with $C_{max}$ reached on average at 0.5 and 0.6 hours after dosage following low and high doses of caffeine, respectively (Table II, Figure 1). Thereafter, caffeine was eliminated with a half-life averaging 4 to 5 hours. Elimination half-life was significantly prolonged, dose-normalized $C_{max}$ was significantly higher, and clearance was significantly lower, following 500 mg as opposed to 250 mg of caffeine. $V_d$ averaged 35 L to 40 L (0.53–0.56 L/kg) and was not related to dose but varied significantly with body weight (Figure 2).

Evaluation of kinetic variables between male and female subjects indicated that gender differences in $V_d$ were explained by body weight; weight-normalized $V_d$ did not differ between men and women. Clearance was significantly higher in men than in women at both doses of caffeine. However, this difference was explained by the confounding effects of cigarette smoking. The two cigarette smokers, both men (Table I), had the highest values of clearance. With these two subjects excluded, there were no apparent effects of gender.

Disappearance of caffeine was mirrored by formation of three metabolites. These were, in order of quantitative importance, paraxanthine, theobromine, and theophylline (Table II, Figure 1).

Self- and observer-ratings of subjective states based on visual analog scales indicated that placebo treatment produced perceptions of calm, peacefulness, normalcy, pleasantness, ease, and relaxation, compared to caffeine; differences among treatments in effect area were significant (Figure 3, Table III). Since these subjective states have not been associated with the caffeine withdrawal syndrome, this syndrome appears not to be influencing subjective response in this study.[8] Caffeine treatment produced significant increases in effect areas of the self-ratings of anxiety, tenseness, elation, unpleasantness, nervousness, excitement, and irritability (Figure 3, Table III). Caffeine also reduced perceptions of sedation and increased perceptions of "thinking speeded up" compared to placebo; however, differences among treatments in effect area were not significant (Table III). Self-ratings of feeling sad, bloated, hungry, seclusive, and contented were not significantly related to treatment condition. At lower doses, caffeine produced significantly greater increases in subjectively favorable ratings of elation, peacefulness, and pleasantness compared to the high dose. Unfavorable subjective ratings (tenseness, nervousness, anxiety, excitement, unpleasantness, and irritability) were greater after high-dose than after low-dose caffeine. Figures 3 and 4 show that subjective effects were maximal during the first 4 hours of treatment.

The somatic symptom rating scales showed significant effects of caffeine in ratings of nausea, perspiration, palpitations, paresthesias, restlessness, and tremor (Table IV, Figure 4). Effects of high-dose caffeine were substantially greater than those of low-dose caffeine or placebo.

Psychomotor performance testing indicated enhanced DSST performance and tapping speed at several time points with low-dose caffeine compared to

**TABLE V**

**Influence of Caffeine and Placebo on 4-Hour Effect Area Measures from Electroencephalogram Results Analyzed by Fast-Fourier Transform***

| Electroencephalogram Measurement | Mean 4-Hour Effect Area | | | F Value (repeated-measures analysis of variance)† |
|---|---|---|---|---|
| | Placebo | 250 mg Caffeine | 500 mg Caffeine | |
| Frontal (Fz) | | | | |
| Beta | 6.94 | −2.63 | 3.48 | 2.33 (NS) |
| Alpha | 1.91 | −4.28 | −1.13 | 1.27 (NS) |
| Total | 11.09 | −10.38 | 2.31 | 1.64 (NS) |
| Central (Cz) | | | | |
| Beta | 8.75 | −3.69 | 6.03 | 10.02 ($P < 0.005$) |
| Alpha | 0.53 | −6.47 | −7.47 | 2.89 ($0.05 < P < 0.1$) |
| Total | 10.34 | −20.13 | −16.47 | 6.69 ($P < 0.01$) |
| Parietal (Pz) | | | | |
| Beta | 10.78 | 1.44 | 1.94 | 4.22 ($P < 0.05$) |
| Alpha | 5.00 | −6.31 | −9.81 | 5.91 ($P < 0.02$) |
| Total | 22.94 | −10.84 | −13.31 | 11.64 ($P < 0.002$) |
| Occipital (Oz) | | | | |
| Beta | 7.66 | 3.19 | 2.12 | 0.64 (NS) |
| Alpha | −0.31 | −0.56 | −12.75 | 0.86 (NS) |
| Total | 8.91 | −2.59 | −20.31 | 1.63 (NS) |

** Effect areas were calculated from change scores (vs. baseline) using the trapezoidal method.*

*† The Student-Newman-Keuls test evaluated differences among individual treatments. Values not underlined together are significantly different ($P < 0.05$). No underlines appear when overall analysis of variance was not significant, in which case no individual differences were significant.*

*NS, not significant.*

placebo (Figure 5). Effects of high-dose caffeine were intermediate.

Caffeine produced small changes in EEG pharmacodynamics relative to placebo. Both doses of caffeine were associated with reduced total, beta, and alpha amplitude compared to placebo (Table V, Figure 6), with no apparent difference between doses of caffeine. Differences among treatments in 4-hour effect area were significant for central and parietal leads, but not for frontal or occipital leads. Electroencephalographic data calculated using relative amplitudes also indicated decreased relative beta activity associated with caffeine, but differences among treatments were not significant.

Plots of pharmacodynamic effects at different plasma caffeine concentration ranges (Figure 7) pooled all concentration–effect points across subjects without regard to time. Each concentration–effect pair represents measurements obtained at the same time. These plots revealed two types of relationships. For subjective variables, such as feeling anxious, nervous, or tremulous, intensity of effect was related to plasma concentration. For DSST and tapping speed, performance improvements relative to placebo were greatest in a plasma caffeine concentration of 2.5 μg/mL to 12.5 μg/mL, then diminished at concentrations exceeding that range.

## DISCUSSION

Caffeine pharmacokinetics in this study were nonlinear, with clearance significantly reduced and elimination half-life prolonged at the 500 mg compared to the 250 mg dose. The lower dose of caffeine produced more favorable subjective effects (elation, peacefulness, pleasantness), whereas the higher dose produced more unfavorable side effects (e.g., tension, irritability, nausea). The lower dose of caffeine improved performance on the DSST and the tapping speed test compared to placebo; high-dose caffeine produced less performance enhancement than the lower dose. The plasma concentration versus response relationship revealed concentration-dependent increases in anxiety and improvements in cognitive and motor performance at low to intermediate concentrations. Both caffeine doses reduced EEG amplitude over the entire 4 Hz to 30 Hz spectrum, as well as in the alpha and beta ranges; however, effects were not dose-dependent. Similar to another study,[19] we showed heterogenous dose–response relation-

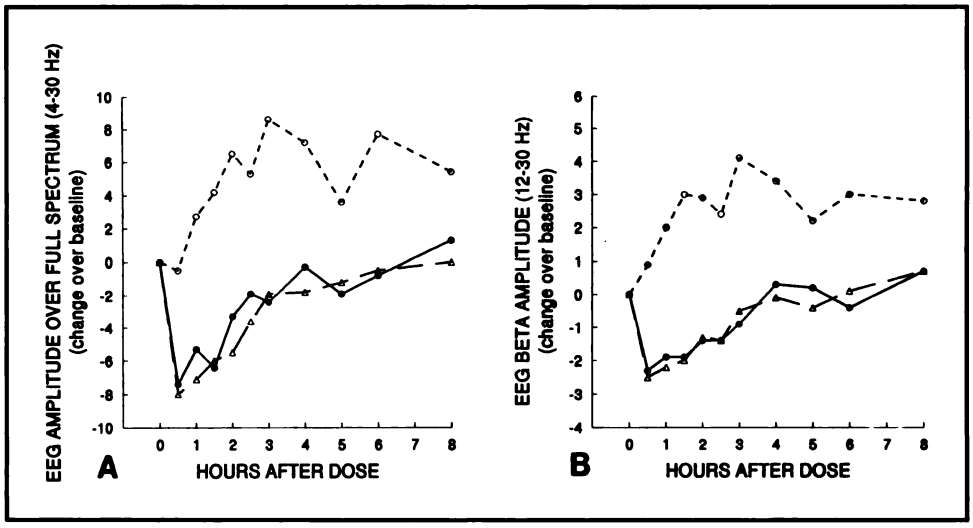


*Figure 6. Effect of placebo (○- -○), 250 mg of caffeine (●–●), and 500 mg (△– –△) of caffeine on total EEG amplitude (4–30 Hz) (A) and on EEG amplitude in the beta (12–30 Hz) range (B), recorded from the central (Cz) lead. Postdosage values represent the increment or decrement over the predose baseline value. Each point is the mean for all subjects at the corresponding time.*

ships for caffeine depending on the pharmacodynamic parameter being measured.

Biotransformation of caffeine in humans is mediated principally by hepatic cytochrome P-450 1A2.[35] The present study demonstrates nonlinear kinetics of caffeine between single oral doses of 250 mg and 500 mg. Some experimental and clinical studies indicate that caffeine kinetics may be nonlinear,[13,36,37] but the mechanism of nonlinearity is not established. *In vitro* studies using human liver microsomes indicate that $K_m$ values for caffeine biotransformation exceed 100 mmol/L, considerably higher than concentrations encountered clinically.[35] Elimination of caffeine was mirrored by formation of three active metabolites, with paraxanthine being the principal product. Since caffeine and its metabolites are similar in potency at adenosine receptors and have similar *in vivo* and stimulant properties, these metabolites may contribute to the net stimulant effect.[11,12,38]

The two individuals with the highest values of caffeine clearance were cigarette smokers, consistent with inducing effects of smoking on human cytochrome P-450 1A2 activity and caffeine clearance.[39] With these individuals excluded, there were no significant gender effects on caffeine kinetics, although the sample size was too small for definitive conclusions to be drawn.

Placebo treatment was associated with favorable subjective responses (calm, peacefulness, normalcy, pleasantness, ease, and relaxation) not usually asso-

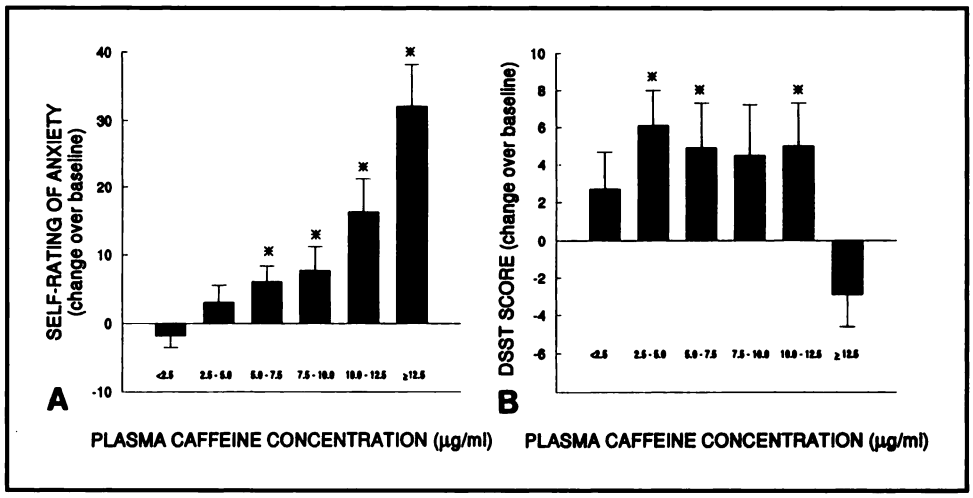


*Figure 7. Relation of plasma caffeine concentration range to change over baseline in self-ratings of anxiety (A) (F = 11.6; P <0.0001) and to change over baseline in digit symbol substitution test (DSST) score (B). Each bar is the mean (± SE) for all subjects within the specified concentration range. (DSST change scores were corrected for placebo-related changes at corresponding times, since placebo treatment was associated with improved performance.) Asterisks indicate a significant difference from zero.*

ciated with the caffeine withdrawal syndrome.[8] The absence of caffeine withdrawal effects could relate to differential timing of the individual subjects' abstinence from caffeine, which was not monitored on an inpatient basis. Caffeine treatment produced clear dose- and concentration-dependent increases in self-ratings of anxiety, tenseness, pleasantness, elation, nervousness, excitement, and irritability. Self-ratings of somatic symptoms indicated greater increases in nausea, sweating, palpitations, restlessness, and tremor at the higher dose. At the lower dose, caffeine produced significantly greater increases in favorable subjective measures of elation, peacefulness, and pleasantness, while the higher dose produced greater increases in anxiety measures. Performance on cognitive and motor tasks was increased relative to placebo at plasma concentrations up to 12.5 mg/mL, whereas drug–placebo differences diminished as concentrations exceeded this range. This is consistent with previous experimental and clinical studies showing disruption of attention, learning, and performance at high doses and concentrations of caffeine.[13–19]

The EEG consequences of caffeine administration in humans have been described previously,[16–19,27] but understanding of the effects of time, dose, and concentration on the human EEG has been incomplete. Despite the clear dose-dependent effects of caffeine on mood and performance, caffeine produced only small changes in the EEG compared to placebo, which did not vary with dose. Total amplitude in the 4 Hz to 30 Hz range was reduced relative to placebo, as was amplitude in the beta frequency range. The findings suggest that analysis of the EEG does not provide data useful for tracking the central pharmacodynamics of caffeine. In contrast, benzodiazepine receptor agonists consistently produce large absolute and relative increases in EEG beta activity, which in turn are consistent with the time course of plasma concentrations and of other clinical pharmacodynamic end points.[29]

The present study was performed using normal volunteers who, in general, were habitual users of caffeine, as is the case with much of the general population. For such individuals, there are limited ranges of caffeine doses and plasma concentrations that are associated with favorable effects on alertness, mood, and performance. In this study, it was demonstrated that low to moderate single doses of caffeine have stimulant and performance-enhancing effects, while higher doses have dysphoric, anxiogenic, and aversive somatic effects. Finally, this study demonstrated that caffeine pharmacokinetics are dose-dependent with greater maximal concentrations, longer half-lives, and lower clearances at higher doses. The dysphoric and somatic effects, as well as performance disruption, from high doses of caffeine may intrinsically limit the doses of caffeine used in the general population and would especially limit caffeine use in populations susceptible to anxiety.

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