The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers

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Abstract

Objective: The purpose of this study was to evaluate the rate of absorption and relative bioavailability of caffeine from a Stay Alert® chewing gum and capsule formulation. Methods: This was a double blind, parallel, randomized, seven treatment study. The treatment groups were: 50, 100, and 200 mg gum, 50, 100, and 200 mg capsule, and a placebo. Subjects consisted of 84 (n = 12 per group); healthy, non-smoking, males who had abstained from caffeine ingestion for at least 20 h prior to dosing and were randomly assigned to the treatment groups. Blood samples were collected pre-dose and at 5, 15, 25, 35, 45, 55, 65, 90 min and 2, 3, 4, 6, 8, 12, 16 and 29 h post administration. Plasma caffeine levels were analyzed by a validated UV-HPLC method. Results: Mean Tmax for the gum groups ranged from 44.2 to 80.4 min as compared with 84.0–120.0 min for the capsule groups. The Tmax, for the pooled data was significantly lower (P<0.05) for the gum groups as compared with the capsule groups. Differences in Tmax were significant for the 200 mg capsule versus 200 mg gum (P<0.05). The mean ka values for the gum group ranged from 3.21 to 3.96 h⁻¹ and for the capsule groups ranged from 1.29 to 2.36 h⁻¹. Relative bioavailability of the gum formulation after the 50, 100 and 200 mg dose was 64, 74 and 77%, respectively. When normalized to the total drug released from the gum (85%), the relative bioavailability of the 50, 100 and 200 mg dose were 75, 87, and 90%, respectively. No statistical differences were found for Cmax and AUCinf for comparisons of the gum and capsule formulations at each dose. Within each dose level, there were no significant formulation related differences in Cmax. No significant differences were observed in the elimination of caffeine after the gum or capsule. Conclusions: The results suggest that the rate of drug absorption from the gum formulation was significantly faster and may indicate absorption via the buccal mucosa. In addition, for the 100 and 200 mg groups, the gum and capsule formulations provide near comparable amounts of caffeine to the systemic circulation. These findings suggest that there may be an
earlier onset of pharmacological effects of caffeine delivered as the gum formulation, which is advantageous in situations where the rapid reversal of alertness and performance deficits resulting from sleep loss is desirable. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Caffeine; Chewing gum; Relative bioavailability; Rate of absorption

1. Introduction

It is well accepted that lack of sleep and fatigue are factors that are associated with degradation in both physical and mental performance, impairment of cognitive functions and alteration of an individual’s mood (Kaplan et al., 1997; Babkoff et al., 1989). Caffeine is commonly used to alleviate the effects of sleep deprivation and fatigue. The pharmacokinetics and pharmacodynamics of caffeine have been well established both at rest (Dews, 1984; Bonati et al., 1982) and under conditions of sleep deprivation (Kamimori et al., 1995, 2000). Penetar and colleagues, in our laboratory at the Walter Reed Army Medical Institute of Research (WRAIR), have demonstrated that caffeine is effective for reversing performance, alertness and mood deficits resulting from prolonged wakefulness (Penetar et al., 1993). These effects have shown to be dose-dependent (Kaplan et al., 1997). Unlike other stimulants, the discriminative and reinforcing effects of caffeine are weak and there is low potential for addiction (Dews, 1984). For this reason caffeine is often the drug of choice for the amelioration of sleepiness resulting from irregular work/rest schedules and sleep deprivation.

The nature of a drug formulation can directly influence its dissolution, as well as its rate and extent of absorption after oral administration. Chewing gum formulations have been evaluated for several drugs including aspirin (Woodford and Lesko, 1981; Bousquet et al., 1992), verapamil (Christurp et al., 1990) and most recently nicotine (Benowitz et al., 1998; Davoli et al., 1998). The gum formulations offer several advantages over the tablet or liquid formulations, such as: (1) most of the drug released from the gum through mastication is believed to be absorbed via the buccal cavity. Absorption through the buccal cavity is considered faster due to its extensive vascularization, especially for low molecular weight hydrophobic agents (Shargel and Yu, 1999). (2) As the onset of drug action in most instances is dependent on speed of delivery, a faster absorption results in a shorter duration for a dynamic response. (3) Drugs absorbed via the buccal cavity bypass intestinal and hepatic first pass metabolism, which potentially increases their extent of absorption (Shargel and Yu, 1999).

Recently, a gum formulation for caffeine, Stay Alert®, has been developed. Bonati et al. have demonstrated that the absorption rate constant ($k_a$) of caffeine is influenced by the characteristic of the dosage form including the pH, volume and composition. In preliminary testing by Novum Inc (Novum, 1998), the absorption rate of caffeine was faster when it was administered in the chewing gum as compared with a standard tablet (Novum, 1998). In this formulation, most of the caffeine could be absorbed via the oral mucosa and its absorption could occur at a faster rate.

The primary objective of this study was to compare the pharmacokinetics (specifically the absorption rate, time to peak concentration, and peak concentration) of three doses (50, 100, 200 mg) of caffeine administered as Stay Alert® chewing gum versus a capsule formulation. Our effort was to evaluate if the chewing gum formulation delivers caffeine at a faster rate than the capsule formulations.

2. Materials and methods

This was a double blind, randomized, single dose, seven treatment, parallel study. Eighty four, non smoking, healthy male subjects (18–35 years) who regularly consumed less than 300 mg of caffeine per day, participated in the study. After signing an informed consent, the health status of subjects was determined on the basis of medical
history, physical examination and routine laboratory tests. The study was conducted at the Walter Reed Army Institute of Research (WRAIR), Silver Spring, MD. The protocol for the study was approved by the WRAIR HSRRB and the HSRRB of the Office of the Surgeon General (US Army).

2.1. Dosing and pharmacokinetic sampling

Two formulations of caffeine were used in this study, capsule and chewing gum. The subjects were randomly assigned to one of seven groups: placebo, 50, 100, or 200 mg of caffeine as chewing gum, and 50, 100, or 200 mg of caffeine in capsule form. A total of 84 subjects were included in the study and each group consisted of 12 subjects. Subjects reported to the lab at 07:00 (Day 1) after a normal night’s rest, having abstained from the use of caffeine, alcohol, or any medications during the previous 12 h. From 07:00 to 23:00 h (Day 1), the subjects were trained on a battery of performance measures (to be described in a separate publication) and had EEG electrodes attached to their head and face. At 23:00 h, an indwelling catheter was inserted into a forearm vein and maintained with a saline drip. At 03:00 h (Day 2), after a 3 h fast, subjects ingested a capsule (caffeine or placebo) and chewed four sticks of gum for 5 min. Each stick of gum contained either 50 mg of caffeine or 0 mg caffeine, corresponding to each individual assigned group. Previous data provided by the manufacturers of Stay Alert® (Amurol Confectioners, Yorkville, IL) indicates that about 85% of the caffeine dose is released in the initial 5 min of chewing (Novum, 1998). During the initial 2 h, subjects remained seated facing a computer console and completed a series of 6 min vigilance tasks (data to be reported elsewhere). After the initial 2 h, intervals between tests increased and subjects were allowed to initiate sedentary activities (e.g. watching television, reading). All activity was discontinued 15 min prior to collection of any data. Blood samples were collected pre-dose and at 5, 15, 25, 35, 45, 55, 65, 90 min and 2, 3, 4, 6, 8, 12, 16 and 29 h post administration. At 21:00 h (Day 2) subjects initiated a 8 h recovery sleep period (21:00 h, Day 2 to 07:00 h, Day 3). At 07:00 h (Day 3) the subjects were awakened, a final blood sample (29 h) was collected, and subjects were debriefed and released. Plasma was immediately separated by centrifugation and stored at −70 °C until analyzed. Subjects received a standardized lunch and dinner and water was available ad libitum.

2.2. Analytical method

To each 250 μl plasma sample were added 250 μl of 0.8 M perchloric acid containing 8 ng/ml of the internal standard, 8-chlorotheophylline. The resulting solution was vortexed for 10 s and centrifuged at 6000 rpm for 5 min. The supernatant was injected into the chromatographic system. The chromatographic conditions were as follows: (1) mobile-phase components consisted of acetonitrile/tetrahydrofuran/acetic acid/water (50:30:5:915 v:v:v:v) (2) Phenomenex C18 analytical column (Waters Millipore Inc, Milford, MA) (1.5 cm × 4.6 mm) along with a C18 guard column (3) injection volume of 100 μl and (4) flow rate of 1.0 ml/min. The HPLC system consisted of a Waters (model 2690) Separations Module and a Waters (model 2487) Dual Wavelength Absorbance Detector (Waters Associates Inc, Milford, MA) set at 274 nm. The system was controlled using MILLennium 32 software. The limit of detection was 100 ng/ml with a within-day variation of less than 5% and a between-day variation of less than 10%.

2.3. Pharmacokinetic modeling and statistical analysis

Non-compartmental and compartmental modeling was used to estimate caffeine pharmacokinetic parameters for a single dose administration. The caffeine concentration-time data were evaluated using WINNONLIN® Professional (Pharsight; Cary, NC, v 3.1). The highest caffeine plasma concentration measured for a subject was the Cmax. The time at which Cmax occurred was the Tmax. The AUC from time 0 to the last concentration time point (AUCcplast) was determined by the trapezoidal method. The AUCinf was determined by the following equation:
AUC_{inf} = AUC_{Cplast} + \frac{C_{Plast}}{\lambda_z} \tag{1}

The AUC_{0-t} for each time point was determined for each group. The elimination rate constant (\lambda_z) was determined by linear regression of the linear portion of the ln (concentration) versus time profile. Typically, four to five points were used to determine the terminal elimination rate constant. Additional pharmacokinetic parameters determined were Vd/F, and Cl/F. Absorption rate constant (k_a) was estimated from the absorption phase by compartmental modeling. In addition, the relative bioavailability (F_R) of the gum formulations at each dose level was determined using the capsule as the reference formulation using the following equation:

\[ F_R = \frac{AUC_{inf}[Gum]}{AUC_{inf}[Capsule]} \tag{2} \]

A parametric general linear model was applied to each of the aforementioned pharmacokinetic parameters. Statistical analysis employed a one-way ANOVA with a Tukey’s post hoc test. Significance was set at the 95% confidence level (P < 0.05).

3. Results

All 84 subjects completed the study with no serious adverse effects. The mean ± S.D. age and weight of the subjects were 23.8 ± 3.6 years and 75.5 ± 13.0 kg, respectively. Fig. 1 illustrates the mean caffeine plasma concentration versus time profile after the 50, 100 and 200 mg capsule and gum treatments. The pharmacokinetic disposition of caffeine in plasma followed a one-compartment model. The pre-dose concentrations of caffeine were below the LOQ of the assay. The estimated pharmacokinetic parameters are summarized in Table 1. Fig. 3 presents the mean ± S.E.M. k_a values and Fig. 4 presents the mean ± S.E.M. C_{max} and AUC_{inf} values after 50, 100 and 200 mg administration of caffeine as gum or capsule.

3.1. Caffeine capsule treatment groups

The mean C_{max} associated with the capsule groups were 1.17, 1.84 and 4.13 mg/l for the 50, 100 and 200 mg doses, respectively. C_{max} increased in a dose-dependent manner, indicating

![Fig. 1. Mean caffeine plasma concentration profiles following a 50, 100 and 200 mg dose of caffeine, as either a capsule or gum formulation to healthy male volunteers. Twelve subjects were enrolled in each of the seven treatment groups.](image-url)
Table 1

Mean (± S.D.) pharmacokinetic parameters following a 50, 100 and 200 mg dose of caffeine as either a capsule or gum formulation to healthy male volunteers

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Pharmacokinetic parameters</th>
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<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (mg l$^{-1}$)</td>
<td>$T_{\text{max}}$ (h)</td>
<td>$\text{AUC}_{\text{inf}}$ (mg l$^{-1}$ h$^{-1}$)</td>
<td>$V_d/F$ (l kg$^{-1}$)</td>
<td>$\text{CL}/F$ (l h$^{-1}$ kg$^{-1}$)</td>
<td>$\lambda_z$ (h$^{-1}$)</td>
</tr>
<tr>
<td><strong>Capsule</strong></td>
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<tr>
<td>50 mg</td>
<td>1.17 (0.98)</td>
<td>1.42 (0.9)</td>
<td>9.63 (8.60)</td>
<td>0.781 (0.208)</td>
<td>0.132 (0.100)</td>
<td>0.15 (0.054)</td>
</tr>
<tr>
<td>100 mg</td>
<td>1.84 (0.70)</td>
<td>1.56 (0.76)</td>
<td>14.7 (7.26)</td>
<td>0.765 (0.375)</td>
<td>0.116 (0.070)</td>
<td>0.162 (0.078)</td>
</tr>
<tr>
<td>200 mg</td>
<td>4.13 (1.92)</td>
<td>2.0 (1.0)</td>
<td>33.5 (13.7)</td>
<td>0.579 (0.259)</td>
<td>0.103 (0.060)</td>
<td>0.18 (0.006)</td>
</tr>
<tr>
<td><strong>Gum</strong></td>
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<tr>
<td>50 mg</td>
<td>0.70 (0.35)</td>
<td>0.73 (0.5)</td>
<td>6.16 (4.83)</td>
<td>1.382 (0.682)</td>
<td>0.20 (0.15)</td>
<td>0.144 (0.072)</td>
</tr>
<tr>
<td>100 mg</td>
<td>1.20 (0.51)</td>
<td>1.25 (0.77)</td>
<td>10.9 (7.0)</td>
<td>1.166 (0.603)</td>
<td>0.171 (0.100)</td>
<td>0.150 (0.048)</td>
</tr>
<tr>
<td>200 mg</td>
<td>3.70 (1.49)</td>
<td>1.34 (1.60)</td>
<td>26.2 (12.2)</td>
<td>0.791 (0.233)</td>
<td>0.143 (0.063)</td>
<td>0.174 (0.090)</td>
</tr>
</tbody>
</table>

Twelve subjects were enrolled in each of seven treatment groups.

linear kinetics. The mean $\text{AUC}_{\text{inf}}$ for the 50, 100 and 200 mg capsule doses were 9.63, 14.7 and 33.5 mg l$^{-1}$ h$^{-1}$, respectively. Again, as seen with $C_{\text{max}}$, the $\text{AUC}_{\text{inf}}$ increased in a linear dose dependent fashion (Fig. 4). For the capsule formulation, the mean $T_{\text{max}}$ ranged from 1.42 to 2.00 h and there were no significant group differences. In addition, the elimination parameters, $\text{CL}/F$, $V_d/F$ and $\lambda_z$ showed no differences statistically across treatment groups. The mean $k_a$ values for the 50, 100 and 200 mg groups are 2.36, 2.06, 1.29 h$^{-1}$, respectively.

3.2. Caffeine gum treatment groups

The mean $C_{\text{max}}$ associated with the chewing gum groups were 0.70, 1.20 and 3.70 mg/l for the 50, 100 and 200 mg doses, respectively. The mean $\text{AUC}_{\text{inf}}$ for the 50, 100 and 200 mg capsule doses were 6.16, 10.9 and 26.2 mg l$^{-1}$ per h, respectively. $C_{\text{max}}$ and $\text{AUC}_{\text{inf}}$ increased in a dose dependent manner (Fig. 4). The time to maximum concentration as indicated by mean $T_{\text{max}}$, ranged from 0.73 to 1.34 h. Even though the mean $T_{\text{max}}$ for the 200 mg dose was almost twice as high as that of the 50 mg dose, this difference was not significantly different. No statistical differences were found for the remaining parameters $V_d/F$, $\text{CL}/F$, and $\lambda_z$. The mean $k_a$ values for the 50, 100 and 200 mg groups are 3.92, 3.21, 3.95 h$^{-1}$, respectively.

3.3. Comparisons of the caffeine gum and capsule groups

Fig. 2 presents a comparison of the caffeine plasma concentration versus time profile for the capsule and gum formulations at the 200 mg doses. Plasma concentrations of other dose groups showed similar profiles. No significant formulation related differences in the extent of drug absorption as measured by $\text{AUC}_{\text{inf}}$ were found, at each dose (Table 1 Fig. 4). In addition, the relative bioavailability of the gum formulation after the 50, 100 and 200 mg dose was 64, 74 and 77%, respectively.

The inset of Fig. 2 presents the differences in mean plasma caffeine concentrations of the gum and the capsule formulations up to 90 min. As seen in the figure, the concentrations for the gum formulations are considerably greater at each time point as compared with the capsule formulation. In addition, the mean $T_{\text{max}}$ ranged from 0.73 to 1.34 h for the gum and 1.42–2.00 h for the capsule formulation. $T_{\text{max}}$ for pooled data was significantly lower ($P < 0.05$) for the gum formulation as compared with the capsule formulation. Furthermore, the post-hoc Tukey’s analy-
sis indicated $T_{\text{max}}$ was significantly lower ($P < 0.05$) for the 200 mg gum (55 min) as compared with the 200 mg capsule (120 min). The $k_{\text{a}}$ between formulations were significantly different ($P < 0.05$). The post-hoc analysis indicated a difference in $k_{\text{a}}$ between 50 and 200 mg gum and capsule groups. There were no significant formulation related differences in the elimination of caffeine.

4. Discussion

The objective of this study was to evaluate the rate and extent of absorption of three doses of caffeine from a gum versus a capsule formulation. The results indicate that the rate of drug absorption is significantly faster ($P < 0.05$) for the gum formulation. Although the bioavailabilities for 50, 100 and 200 mg gum groups are reported as 64, 74, and 77%, these bioavailabilities were based on 100% release of caffeine from the gum. However, data from the manufacturers (Amurol Confectioners) indicates that only 85% of the caffeine is released from the gum following 5 min of chewing (Novum, 1998). Based on an 85% dose the mean bioavailabilities may be 75, 87, and 90% for the 50, 100, and 200 mg groups, respectively. It appears that for the 100 and 200 mg groups, the gum and capsule formulations provide a near comparable amount of caffeine to the systemic circulation. These findings suggest that both physical and mental performance deficits resulting from sleep loss or fatigue could be more quickly

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![Graph](image_url)

Fig. 2. Mean caffeine plasma concentration profiles following a 200 mg dose of caffeine as a capsule or gum formulation to healthy male volunteers. Twelve subjects were enrolled in each of the two treatment group. Inset shows plasma concentration profiles of 200 mg dose as capsule or gum up to 90 min after administration of caffeine.
reversed by caffeine administered in a chewing gum formulation compared with a capsule formulation.

Coffee and cola are the typical forms in which most individuals can obtain caffeine. Stay Alert® chewing gum was developed by Amurol Confectioners (Yorkville, IL) as a means to provide a quick and convenient source of caffeine in a portable form. Absorption in a gum formulation occurs primarily through the buccal mucosa, a well accepted method of increasing the rate of drug absorption (Shargel and Yu, 1999). The buccal mucosa has a rich vascular supply resulting in favorable rate of absorption of a drug, especially for lipophilic agents, like caffeine. In this study, we observed a quicker rate and a near comparable extent of absorption for caffeine administered as chewing gum versus a capsule formulation. Absorption of several other pharmacological agents when delivered in a gum formulation has been evaluated. Bousquet et al. (1992) examined the relative bioavailability of aspirin in two gum formulations (480 mg), as compared with a standard tablet formulation in ten healthy male volunteers. The two gum formulations showed a significantly lower $T_{\text{max}}$ than the tablet, but also showed a lower $C_{\text{max}}$. It was concluded that aspirin administered in a gum formulation has a faster absorption but a lower extent of absorption. Our results were very similar in that we observed a significant increase in the rate of absorption of caffeine in the gum formulation. We also observed a trend toward a lower $C_{\text{max}}$ for the caffeine gum formulation, but it did not reach statistical significance. Previous research has shown that the relative bioavailability of a drug is not significantly different when administered in a gum formulation. For example, Christopher et al. (1990) found no difference in the relative bioavailability of methadone in a 20 mg gum versus a tablet formulation in seven healthy volunteers. They also stated that methadone was absorbed through the buccal mucosa as well as through the GI tract when swallowed in the saliva. The present results with caffeine are consistent with those previous findings.

Although the caffeine delivered through the gum formulation was intended to be absorbed through the oral mucosa, the use of four sticks of gum may have resulted in increased salivation (due to the large size of the gum cud) and a corresponding increase in the portion of the drug being swallowed with the saliva. The portion of caffeine swallowed in the saliva would be absorbed in the gastrointestinal tract, just like a capsule. In fact, we did observe multiple peaks in the plasma profiles of a number of subjects corresponding to multiple sites of absorption. Dual absorption sites could result in an immediate increase in plasma caffeine levels via absorption through the oral mucosa, followed by another peak corresponding to subsequent absorption in the gastrointestinal tract. However, this may have contributed to the high variability of the pharmacokinetic parameters, indicated by their high standard deviations. High variability could have also resulted from a parallel design of the study. Although a cross over study would have been the most elegant design, it was technically difficult. If the study was performed with a cross over design, there was an element of learning in the pharmacodynamic tasks that the subjects were asked to perform. Additionally, the subjects would alter their sleep pattern before their second study date based on their experience with the first study date. This would introduce bias and errors in the pharmacodynamic measurements.

Pharmacodynamic effects of caffeine are dependent on its pharmacokinetic properties. A quicker rate of absorption (Table 1 and Fig. 3), as observed with the gum could result in quicker onset of its stimulant effects. Caffeine improves performance and alertness in sleep deprived subjects, and in individuals who are required to work through the nadir of the circadian rhythm of alertness and performance in the early morning hours (e.g. medical and emergency personnel, long haul truckers, and shift workers) (Akerstedt and Ficca, 1997; Reyner and Home, 1998). As the onset of action for the gum delivery is within 5–10 min of administration, the dose of caffeine can be quickly and easily titrated. A second stick can be immediately administered, if a higher dose is necessary. In contrast, the initial dose in a tablet or liquid formulation would require between 30 and 45 min before a decision can be
made about the need for another dose which itself would take 30–45 min more to reach \( C_{\text{max}} \). Furthermore, the act of chewing gum itself has been shown to increase alertness in night shift workers by Hodoba et al. (Hodoba, 1999). In the study, sleepiness was assessed in 21 student volunteers and 60 medical professionals, with corresponding controls, before and after chewing gum (without drug) by the Stanford Sleepiness Scale (SSS). It was reported that the group that chewed gum had a lower score on the SSS indicating a greater level of alertness. This could add to the pharmacodynamic effects of caffeine when administered in the gum formulation and provide more improvement in alertness.

In summary, caffeine administered in the chewing gum formulation was absorbed at a significantly faster rate while its bioavailability was near comparable to that of the capsule formulation for the 100 and 200 mg dose groups. Consequently, Stay Alert® chewing gum is a convenient and effective means of rapidly administering caffeine and may prove useful in ameliorating the effects of mental or physical fatigue associated with sleep deprivation or shift work.

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Fig. 4. Mean (±S.E.M.) $C_{max}$ and AUC values following 50, 100 and 200 mg dose of caffeine as a capsule or gum formulation in healthy male volunteers. Twelve subjects were enrolled in each of the seven treatment groups.

References


