Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine

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Received 8 March 2005; received in revised form 5 August 2005; accepted 9 August 2005

Abstract

Aims: Two tablet formulations of buprenorphine (a buprenorphine mono-product, Subutex® , and a buprenorphine/naloxone combination product, Suboxone® ) are available for use in the treatment of opioid addiction; however, the bulk of the clinical studies supporting its approval by the US Food and Drug Administration (FDA) were conducted with a sublingual liquid preparation. To assist the clinician in interpreting the relevant literature in establishing dosing parameters for prescription of tablet buprenorphine, this study was designed to compare the steady state: (1) pharmacokinetics and bioavailability, and (2) physiological, subjective and objective opiate effects of two 8 mg buprenorphine tablets (16 mg) to those of 1 ml (8 mg/ml) buprenorphine solution based upon early reports suggesting that the bioavailability of the tablet was approximately 50% of that of the liquid.

Design: Randomized, open-label, two-way crossover study.

Setting: Inpatient hospitalization for 21 days.

Participants: Twenty-four male and females in general good health and meeting DSM-IV criteria for opiate dependence.

Intervention: Subjects received one of the two buprenorphine formulations in the first 10-day period, and the other for the second 10-day period with no washout.

Measurements: Pharmacokinetic analyses, opiate effects and adverse events.

Findings: Drug steady state was reached by Day 7 of each 10-day period, area under the curve for 16 mg (two 8 mg) tablets was higher than the solution. The only non-kinetic statistically significant difference observed between the formulations was in changes in total opioid agonist score.

Conclusions: The serum concentration achieved by 16 mg of tablet buprenorphine is higher than that of the 8 mg solution, although differences between physiologic, subjective and objective opioid effects were not noted. The relative bioavailability of tablet versus solution is estimated to be 0.71; thus, with respect to dosing parameters for the tablet, clinicians should consider using less than 16 mg to achieve bioequivalence to the 8 mg solution.

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Keywords: Buprenorphine; Bioavailability; Pharmacokinetics

1. Introduction

The availability of buprenorphine for the outpatient treatment of opioid addiction (Resnick, 2003) represents a landmark event in the field of addiction treatment in the United States. Scheduled so that it may be dispensed by physicians in their private offices, buprenorphine is the first real alternative to the methadone clinic available to patients seeking pharmacologic treatment for addiction to heroin or prescription opioids (Leshner, 2003; Ling and Smith, 2002). After nearly eight decades, US physicians are able to again use an opioid to treat patients with opioid addiction, despite buprenorphine for this indication having been available considerably longer in Australia and in Europe, most notably in France where it had been approved since 1995. Multiple carefully controlled clinical trials have established the dosing parameters, unique safety and good-efficacy of buprenorphine (Barnett et al., 2001; Giacomuzzi et al., 2003; Ling and Wesson, 2003; West et al., 2000). Due to its partial agonist properties, a ceiling
effect exists for its agonist properties, and unlike methadone or LAAM, it produces what appears to be a low level of physiological dependence with minimal withdrawal symptoms (Walsh and Eissenberg, 2003).

As currently marketed, buprenorphine is formulated as a sublingual (SL) tablet in two forms, a mono-product (Subutex®) containing buprenorphine alone, and a combination product (Suboxone®) combined with naloxone to discourage parenteral misuse. Most of the studies conducted by European and Australian investigators have used the tablet mono-product Subutex® and most recent studies by US investigators have used the combination tablet Suboxone®. The bulk of the early investigations, mostly conducted in the US, and the pivotal clinical trials supporting buprenorphine’s approval by the US Food and Drug Administration (FDA) were conducted using a SL solution, which is known to be not strictly bioequivalent to the tablet formulation (Walsh and Eissenberg, 2003).

Previous single-dose pharmacokinetic (PK) studies comparing buprenorphine sublingual tablets with solution formulations have shown that the extent of bioavailability of the tablet formulation (8 mg) was quantitatively less than that of the solution formulation (8 mg/ml) (Nath et al., 1999). The bioavailability of one 8 mg buprenorphine sublingual tablet was approximately 50% (range 24–74%) relative to 1 ml of 8 mg/ml buprenorphine sublingual solution, and unrelated to salivary pH. In comparison to the liquid, the tablet also produced significantly fewer opioid agonist effects, although the same degree of opioid antagonist effects. Similarly, in two studies using more chronic dosing paradigms, plasma concentrations of the 8 mg tablet were estimated to be 55% of those of the solution after 7 days of dosing (Schuh and Johanson, 1999), and 62% after 14 days of dosing (Strain et al., 2004).

The present study was designed to test the estimated 50% relative bioavailability for the tablet in comparison to the solution, as demonstrated in acute- and chronic-dose studies. Evaluated were the steady-state pharmacokinetics and bioavailability of buprenorphine following multiple administrations (10 days) of two 8 mg buprenorphine SL tablets in comparison to 1 ml of 8 mg/ml SL solution. Further, evidence of physiological, subjective and objective opioid agonist and antagonist responses to the tablets versus solution was documented.

2. Methods

2.1. Design

The study used an open-label, randomized, two-way crossover design and was conducted in an inpatient setting over 21 days. Twenty-four subjects were randomized to receive one of two treatments (two 8 mg tablets SL QD or 1 ml of 8 mg/ml solution SL QD) for the first 10-day period and the other treatment for the second 10-day period with no washout period between treatments. Plasma samples for PK analysis were taken prior to dosing Days 7–10 of each treatment period, and at specified intervals for 24 h following dosing on Day 10 of each treatment period. Subjective and physiologic effects were measured daily during both treatment periods, and again at specific time points following dosing on Day 10 of each treatment period.

2.2. Subjects

Subjects were recruited from the local community by referral and advertisement. Male and female adults 21–55 years of age who met DSM-IV criteria for opiate dependence were eligible to participate, provided they were not dependent on other substances (except caffeine and nicotine), and were in good general mental and physical health. All potential subjects entered the Institutional Review Board-approved study only after providing full informed consent. Female subjects were required to have a negative pregnancy test and to agree to use adequate birth control throughout the study.

Subjects were permitted to drop out of the study at any time if they so desired, or if the investigator felt to do so was clinically appropriate. Substitute subjects were enrolled for those who discharged early, keeping the sample size of completed subjects at 24. Data from discontinued subjects who received at least one dose of buprenorphine were retained and inspected for adverse events.

2.3. Materials and methods

The buprenorphine tablets (without naloxone) were manufactured by Reckitt and Colman (Hull, United Kingdom) and the buprenorphine solution (buprenorphine hydrochloride in 30% ethanol) was manufactured by Carolina Medical Products Company (Farmville, NC). Medication was supplied by Research Triangle Institute and shipped directly to the institutional pharmacy.

2.3.1. Measures

2.3.1.1. Pharmacokinetics. Blood samples for buprenorphine analyses were taken just prior to dosing on Days 7–10 and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h after dosing on Day 10 of both periods. Day 10 sampling took place via an intravenous catheter. Ten milliliters of blood was extracted at each time point, centrifuged within 15 min and the plasma was stored at −70°C prior to analysis via liquid chromatography/tandem mass spectrometry (Moody et al., 2002).

2.3.1.2. Physiologic measures. Vital signs (heart rate, sitting blood pressure, temperature and respiration rate) and pupil diameter were measured daily during the study just prior to buprenorphine dosing, after the subject had sat quietly for 10 min, and had refrained from caffeine and nicotine for at least 30 min. On study Day 10, vital signs (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h) and pupillary photographs (1, 3, 6, 12, 24) were collected for each treatment period following buprenorphine dosing. Also, prior to dosing, saliva was collected in a test tube to evaluate the effect of salivary pH on rate of tablet dissolution.

2.3.1.3. Opioid effects. Prior to dosing, and at specified time points following dosing on Day 10 (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h), subjects were asked to rate their current...
Adverse effects

- **Global intoxication and withdrawal scale**: Subjects rated feelings of opioid intoxication and opiate withdrawal on scales of 0–100, where 0 indicated no effect and 100 the maximum intensity of symptoms experienced after using opiate drugs.

- **Opiate visual analog scale**: Subjects rated each of four drug effects (‘good’ drug effect, ‘bad’ drug effect, drug liking and sickness) by making a vertical mark along a 100 mm line marked at opposite ends as ‘not at all’ (0 mm) and ‘extreme’ (100 mm).

- **Opiate agonist effects scale**: Subjects rated the degree to which they experienced each of 16 typical opiate-like effects (nodding, heavy or sluggish feeling, dry mouth, good mood, energetic, upset stomach, itchy skin, relaxed, coasting, talkative, pleasant sickness, drive, carefree, drunken, friendly, nervous) on a scale of 0 (not at all) to 4 (extremely). Scale scores range between 0 and 64 points.

- **Opiate withdrawal scale**: Subjects rated the degree to which they experienced each of 21 typical opiate withdrawal symptoms (muscle cramps, flushing, painful joints, yawning, restless, watery eyes, runny nose, chills or gooseflesh, sick to stomach, sneezing, abdominal cramps, irritable, backache, tense and jittery, sweating, depressed, sleepy, shaky, tremulousness, hot or cold flushes, bothered by noise, skin clammy and damp) on a scale of 0 (not at all) to 4 (extremely). Scale scores range between 0 and 84 points.

A trained member of the research team concurrently evaluated the subject’s symptoms on the opiate agonist effects scale and the opiate withdrawal scale, and also completed the:

- **Opiate withdrawal intensity scale**: The observer rated the presence and severity of six opiate withdrawal signs (lactation, rhinorrhea, yawning, perspiration, piloerection, restlessness) on a scale of 0 (not at all) to 2 (extremely). Scale scores range between 0 and 24.

- **Adverse effects**: Subjects were monitored for adverse events throughout the entire study period by trained study staff. The investigator or designated staff evaluated the intensity, seriousness and causal relationship to the study medication(s) of all adverse experiences.

### 2.3.2. Procedures

Subjects who appeared to be eligible to participate on the basis of a telephone interview underwent a screening visit following informed consent during which time they received a physical and psychiatric examination and clinical laboratory testing. A drug use history for the previous 6 months was also collected.

For study participation, subjects were admitted to the inpatient ward the morning of the day before their first buprenorphine dose, where they remained as inpatients until 24 h after the final dose. They were housed in a locked ward and were attended by a study staff member when not on the ward. Only certain concomitant medications (Tylenol, Mylanta, Maalox, Milk of Magnesia, Immodium) were provided to subjects as needed and recorded in the study casebooks. They received a low fat breakfast each morning at 7:30 a.m. and received the study medication at 9:00 a.m. The first day of the first treatment period, all subjects received a half dose of the formulation to which they were assigned (1 ml of 4 mg/ml solution if assigned to liquid, one 8 mg tablet if assigned to tablet), and received a full dose for the remainder of the study. When receiving the solution medication, subjects were instructed to hold the sublingual medication under the tongue for 5 min and then swallow; for the sublingual tablets, subjects were instructed to keep the medication under the tongue until it completely dissolved or for 15 min, which ever occurred sooner, and then swallow.

### 2.4. Data analysis

To verify that steady state was attained, the predose plasma buprenorphine concentration (C0) on Days 7, 8, 9 and 10 was examined. A repeated-measures ANOVA was used, with subject as the between-subject factor and treatment and day as the within-subject factors. Tests for a linear trend and multiple comparisons between days were performed. The bioequivalence analysis was performed on both the log-transformed and actual values of AUC0–24h, maximum concentration (Cmax) and time to maximum concentration (Tmax). A standard crossover model that included period and treatment as within-subject factors and sequence as a between-subject factor was used to analyze the PK parameters. Bioequivalence was assessed using one-sided tests with 5% type I error. If the 90% confidence interval of the ratio of the log-transformed AUC or Cmax for the two formulations was within the range of 0.80–1.25, the two formulations were considered to be bioequivalent.

The change from baseline (predose value on Day 10) for each physiologic measure collected following dosing on Day 10 of both periods was analyzed. Two change scores were calculated for both the subject and observer opiate effect measures: change from predose Day 10 baseline and each measure collected following dosing. All change scores were analyzed with a repeated-measures ANOVA model that contained the effects of sequence, treatment, time and subject, and interactions between sequence and treatment, time and treatment, subjects and treatment, subject and time, and sequence, treatment and time. AUC analysis was also conducted on the total scores on the subject and observer opiate agonist effects scale and the opiate withdrawal scale. Differences between the formulations were compared. All adverse experiences reported by the subjects were coded using the COSTART dictionary and inspected for severity, frequency, body system and relationship to treatment. To describe the relationship between salivary pH and rate of tablet dissolution, data were examined with a t-test to determine if there was a difference in mean saliva pH for tablets which dissolved within 5 min or after 5 min.
3. Results

A total of 34 subjects enrolled in the study; of the 10 subjects who discontinued prematurely, 4 withdrew at their own request and 6 were discharged due to protocol non-compliance. Adverse event data were collected from the nine discharged subjects who had received at least one dose of buprenorphine. Demographic characteristics of 24 subjects who completed the study are summarized in Table 1.

3.1. Pharmacokinetic analysis

On Days 7–11 of both periods (where “Day 11” refers to the 24-h post-dose assessment on Day 10), the mean predose concentration for the solution varied between 0.87 and 0.98 ng/ml, and the mean concentration for the tablet varied between 1.59 and 1.75 ng/ml. There were neither significant differences between days nor a significant linear trend, indicating that steady state was attained by Day 7. Mean plasma levels of buprenorphine on Day 10 of both periods are summarized by time and treatment in Fig. 1. For both formulations, a second, small increase in blood level was noted approximately 8–12 h following dosing.

Descriptive statistics for the PK data for each formulation, and the 90% confidence intervals for the ratio of the two formulations with respect to AUC and $C_{\text{max}}$ (analyzed on log-transformed or untransformed scales) are detailed in Table 2. No sequence effect or period effect was observed in any of the crossover analyses for AUC and $C_{\text{max}}$. As can be seen, the upper limit of the 90% confidence interval for each of the four parameters is higher than 1.25, thus the two treatments are not bioequivalent.

Based upon these data, the relative bioavailability of an equal dose of 8 mg buprenorphine for the tablet versus solution was calculated. The 8 mg buprenorphine tablet contains 8.62 mg buprenorphine HCl; therefore, the adjusted blood concentrations for the tablet formulation were: adjusted Conc. = Conc. × 8/(8.62 × 2). The crossover analysis was also performed on the adjusted AUC$_{(0-24)}$ and $C_{\text{max}}$ values. The estimated relative bioavailability of the 8 mg tablet versus 8 mg solution is 0.71, with 90% confidence intervals (0.64–0.79). The relative $C_{\text{max}}$ of tablet versus solution is 0.63, with 90% confidence intervals (0.55–0.73). These estimates of bioavailability should be taken with caution; however, as the adjustment procedure used to obtain the estimates had an underlying assumption of dose proportionality.

3.2. Physiologic and opiate effects

Day 10 mean post-dose values for all physiologic measures in both periods were within normal range for both formulations, and all measures returned to their approximate predose values within 24 h after dosing. With both formulations, pupil diameter

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Table 1
Demographic characteristics of study participants (n = 24)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T-S (n = 12)</th>
<th>S-T (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male 8</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Female 4</td>
<td>2</td>
</tr>
<tr>
<td>Age (year)</td>
<td>Mean 33.5</td>
<td>41.1</td>
</tr>
<tr>
<td></td>
<td>S.D. 6.5</td>
<td>28.4</td>
</tr>
<tr>
<td>Race</td>
<td>White 7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Latino 5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Black 0</td>
<td>1</td>
</tr>
<tr>
<td>Height (in.)</td>
<td>Mean 67.1</td>
<td>70.2</td>
</tr>
<tr>
<td></td>
<td>S.D. 3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>Mean 146.8</td>
<td>150.3</td>
</tr>
<tr>
<td></td>
<td>S.D. 23.5</td>
<td>28.4</td>
</tr>
</tbody>
</table>

T-S, subjects crossing over from tablet to solution buprenorphine; S-T, subjects crossing over from solution to tablet buprenorphine. Crossover occurred at Day 10 with no washout period between treatments.

Table 2
Pharmacokinetic parameters for solution and tablet buprenorphine with 90% confidence intervals

<table>
<thead>
<tr>
<th></th>
<th>Solution</th>
<th>Tablett</th>
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<tr>
<td>AUC (ng/ml h)</td>
<td>C$_{\text{max}}$ (ng/ml)</td>
<td>$T_{\text{max}}$ (h)</td>
</tr>
<tr>
<td>Mean</td>
<td>46.37</td>
<td>7.87</td>
</tr>
<tr>
<td>S.D.</td>
<td>16.15</td>
<td>3.15</td>
</tr>
<tr>
<td>CV (%)</td>
<td>34.8</td>
<td>40.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>23.26</td>
<td>2.40</td>
</tr>
<tr>
<td>Maximum</td>
<td>69.75</td>
<td>14.04</td>
</tr>
</tbody>
</table>

Estimated ratio (tablet/solution) 90% Confidence intervals

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>$\ln$(AUC)</td>
<td>1.53</td>
</tr>
<tr>
<td>$\ln(C_{\text{max}})$</td>
<td>1.36</td>
</tr>
<tr>
<td>$\ln(T_{\text{max}})$</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Plasma samples for analyses were taken prior to dosing on Days 7–10 of each treatment period, and at specified intervals after dosing at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h following dosing on Day 10 of each treatment period.
and heart rate decreased slightly, systolic and diastolic blood pressure increased slightly, and respiratory rate and temperature showed little variance. The ANOVA showed that there were no significant effects of treatment on any of the physiologic measures.

For most of the subject-reported opiate effects, mean scores were low prior to dosing and did not change greatly after dosing on Day 10. In general, over the course of 24 h, slight increases in intoxication, “good drug effect” and “drug liking” peaked and a slight decrease in withdrawal ratings were noted 2–4 h post-dosing, while “bad drug effect”, “sickness” and withdrawal severity all increased 6–8 h post-dosing. The only non-kinetic measure on which a significant difference between treatment was noted was the total opiate agonist effects scale; for both formulations there was an initial increase in observed withdrawal severity were noted 8–14 h after dosing, with a slight decrease in scores in the case of the tablet immediately following dosing.

3.3. Adverse events

Table 3 provides summary data on the treatment-related adverse events noted for each formulation. Percentages of treatment-related adverse events were similar between the tablet (82.8%) and the solution (85.7%) formulations of buprenorphine, as were rates of those considered severe adverse events (tablet 62.1% versus solution 57.1%). Adverse events were predominately described as affecting the body as a whole, with headache being the most common symptom and considered to be treatment-related in 34.5% of subjects taking the tablet and 28.6% of the subjects taking solution. No serious adverse events occurred during the study.

3.4. Effects of salivary pH

No significant difference in salivary pH was noted between subjects whose tablets dissolved within 5 min (pH 6.40) and after 5 min (pH 6.50). Overall, 37% of the subjects had to swallow the undissolved pill after 15 min on between 3 and 7 occasions during the 10-day treatment.

4. Discussion

Although most of the early clinical studies of buprenorphine for the treatment of opioid addiction had been conducted by US investigators, its approval by the US Food and Drugs Administration (FDA) was slow. It literally took an act of congress in the form of the Narcotic Treatment Act of 2000 to make buprenorphine available considerably longer, and a number of clinical studies were conducted by European and Australian addiction has been available considerably longer, and a number of clinical studies were conducted by European and Australian investigators using the mono-product Subutex®, while recent studies by US investigators have used the combination product Suboxone®. The bulk of the early research and the pivotal clinical trials providing critical data for its eventual approval by the FDA had used a liquid formulation of buprenorphine, which was known to have different bioavailability from the marketed tablets. To enable clinicians to properly interpret the body of research, it was necessary to determine the relative bioavailability of the tablet and the liquid formulations. The study results reported here was part of that effort.

An initial single-dose study had estimated the bioavailability of the tablet to be approximately 50% that of the liquid, and provided the rationale to compare the tablet formulation at twice the dose of the liquid so as to achieve comparable blood concentration in the two treatment groups, although subsequent studies...
have shown that the blood concentration of the tablet formulation increased with repeated dosing. Data from the study reported here provide evidence for the lack of bioequivalence of 1 ml of 8 mg/ml buprenorphine and 16 mg (2 mg × 8 mg) buprenorphine tablets, as had been expected based upon the earlier studies. The tablet formulation at twice the dose of the solution achieved higher mean predose plasma concentration levels, a greater AUC (0–24), and a higher C_{max} than the solution, although the T_{max} was similar between the two formulations, as was the shape of 24 h plasma concentration curve. Despite higher plasma concentrations in the tablet condition, the percentages of adverse events were not different between the two formulations.

These data collected after 10 days of buprenorphine dosing are not unlike those reported by Strain et al. (2004) after 7 days of dosing, with respect to tablet versus solution AUC (64%) and peak plasma concentration (62%). These investigators did find that with a longer period of dosing (14 days), the bioavailability of the tablet increased with respect to the solution (AUC = 70%, C_{max} = 73%), primarily due to a decrease in the pharmacokinetic efficacy of the solution with the passage of time. Examination of buprenorphine plasma concentrations over Days 7–10 of each treatment period in the present study did not reveal a clear trend toward decreased values for the solution over time. Strain et al. (2004) suggest that an “adaptation of the buccal environment to the solution form relative to the tablets” (p. 41) may occur and be related to the alcohol used on the solution formulation, the concentration of which was higher in the Strain study (40%) than in the present work (30%), and accounting for a lack of a time effect.

Despite the significant differences in bioavailability between the tablet and solution formulations, differences between physiologic, subjective and objective opioid effects were less distinct. Although observer and subjective assessment was unblinded, no differences between treatments were noted in opioid effects over the course of the study; vital signs were normal and intoxication/withdrawal symptoms were minimal. The Day 10 measures showed small but predictable opiate agonist effects with both formulations on both physiologic and subjective indices, with agonist effects predominating in the first few hours after dosing and dysphoric and withdrawal symptoms following 6–8 h later. The general trend for a greater agonist effect on physiologic measures with the tablet is consistent with the higher blood concentration levels. The tablet significantly differed from the solution on the subjective total opiate agonist effects scale only, on which subjects on solution reported higher and more variable opiate agonist, despite the lower blood concentration achieved.

The physiologic measures are reassuring in that they showed little fluctuation between peak and trough concentrations, confirming the high safety profile of buprenorphine with chronic treatment, especially with regard to respiratory depression. These findings indicate that a steady state is achieved after about 7 days of dosing with the tablet containing approximately 70% blood concentration of the equivalent liquid doses. This level is considerably higher than suggested by the results of the early single-dose studies, and consistent with subsequent findings from chronic dosing studies (i.e. Schuh and Johanson, 1999; Strain et al., 2004), that bioavailability of the two formulations approach each other with chronic dosing. Thus, the initial suggestion that tablets need to be given at twice the milligram dose of the liquid is disputed.

This study was conducted before the development of the buprenorphine/naloxone combination tablet (Suboxone®). The tablets used in this study were provide by the manufacturer and were identical to the subsequently marketed mono-product tablet Subutex® (Chris Chapleo, Reckitt Benckiser, personal communication, 29 July 2005). The tablets were administered by instructing participants to hold the tablets under the tongue until they completely dissolved or until 15 min had elapsed before the participants were allowed to swallow. This was the practice subsequently adopted in the clinical dosing guidelines. While swallowing the small amount of residual tablets may have some minor effect on the total concentration achieved, it is reassuring to note that it would, if anything, further increase the blood concentration of the tablets and would not have altered the conclusions of the trial.

Acknowledgements

This work was supported by a medication development center grant from NIDA. Reckitt/Benckiser, manufacturer and owner of buprenorphine products provided the study material for this study. Walter Ling has served as consultant to Reckitt/Benckiser and Reckitt/Benckiser has given UCLA an unrestricted educational grant to support his work. The analytical work was performed under funding from the National Institutes on Drug Abuse, National Institutes of Health Contract No. N01DA-1-9205 and N01DA-7-8074.

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