Buprenorphine tablet versus liquid: A clinical trial comparing plasma levels, efficacy, and symptoms

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Abstract

We evaluated peak plasma concentrations, trough concentrations, and the 24-hour area under the concentration curve (AUC0–24 h) during maintenance with sublingual (SL) liquid or tablet formulations in 57 opiate-dependent volunteers. Study participants were assigned randomly to one of three SL daily buprenorphine dose pairs and maintained for 2 weeks with the liquid formulation followed by 2 weeks with the corresponding tablet dose. Plasma samples were obtained after at least 10 days of maintenance with the liquid formulation and after at least 10 days of that with the tablet formulation. The bioequivalence of the tablet compared with the liquid doses ranged from 57% to 75% based on peak concentrations, from 102% to 108% based on trough concentrations, and from 66% to 86% based on 24-hour AUC, but there was a large intersubject and intrasubject variability in plasma concentrations, with greater variability following tablets than liquid. Measures of withdrawal symptoms or illicit opioid use were not associated with buprenorphine dose, formulation, or plasma buprenorphine levels.

Keywords: Buprenorphine; Plasma concentration; Substance abuse; Opioid maintenance

1. Introduction

The efficacy of buprenorphine for the maintenance treatment of opioid dependence is dose dependent, and daily doses of 8–16 mg of sublingual (SL) liquid are generally well tolerated and more efficacious than lower doses (Bickel et al., 1988; Fudala et al., 2003; Johnson et al., 2000; Johnson, Jaffe, & Fudala, 1992; Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Ling et al., 1998; Mattick, Kimber, Breen, & Davoli, 2002; Mello & Mendelson, 1980; O’Connor, Chawarski, Pakes, & Schottenfeld, 1998; Schottenfeld, Pakes, Oliveto, Ziedonis, & Kosten, 1997; Strain, Stitzer, Liebson, & Bigelow, 1994). Most studies establishing the efficacy of buprenorphine for opioid agonist maintenance treatment and evaluating buprenorphine dose-dependent effects were conducted using an SL alcohol-based liquid preparation of buprenorphine. Two tablet formulations, containing either buprenorphine only (mono tablet) or buprenorphine combined with naloxone in a 4:1 ratio (combination tablet), have been developed and are approved for maintenance treatment. Consequently, it is important to establish the bioequivalence of the tablet and liquid formulations to provide clinical guidelines in dosing using the tablets.

The primary goal of this study was to assess the bioequivalence of buprenorphine mono tablets as compared with liquid buprenorphine by comparing plasma buprenorphine concentrations following SL administration of buprenorphine solution and buprenorphine mono tablets. Initial studies indicated that the bioequivalence of the tablets is 50–60% of the liquid, suggesting that tablet doses would need to be approximately double the liquid dose to achieve comparable plasma concentrations (Mendelson, Upton, Everhart, Jacob,
& Jones, 1997; Mendelson, Upton, & Jones, 1996; Nath et al., 1999). However, newer studies reported somewhat higher bioequivalence values of the buprenorphine tablets that range from 52% to 83% (Schuh & Johanson, 1999; Strain, Moody, Stoller, Walsh, & Bigelow, 2004). A potential limitation of these studies was that they only evaluated a single 8-mg tablet dose, which is at the lower end of doses used in clinical practice, administered either on a single occasion (Mendelson et al., 1997; Nath et al., 1999) or chronically for 7–14 days (Schuh & Johanson, 1999; Strain et al., 2004). Another recent study (Harris, Mendelson, Lin, Upton, & Jones, 2004), using a between-subject design, compared a range of liquid buprenorphine doses (4–32 mg) with buprenorphine-only and buprenorphine/naloxone tablet doses (4–16 mg), with liquid and tablet doses administered on a single occasion. This study reported a lower bioavailability of buprenorphine tablets (50–64%) compared with buprenorphine solution but comparable trough plasma concentrations for both buprenorphine tablets and solution at 24 hours after administration.

This study compared three buprenorphine SL liquid and tablet dose pairs—(1) 8-mg liquid and two 8-mg tablets; (2) 12-mg liquid and three 8-mg tablets; and (3) 16-mg liquid and four 8-mg tablets—in a large sample (N = 57) of opiate-dependent volunteers. The liquid dose was administered daily for 2 weeks and was then followed by daily administration of the tablet dose for 2 weeks. The liquid dose was equivalent to doses commonly used in efficacy studies (8, 12, or 16 mg), and the tablet dose was twice the liquid dose.

2. Materials and methods

2.1. Subjects

Sixty-one opiate-dependent volunteers were recruited from a group of subjects completing an outpatient clinical trial comparing the efficacies of daily and thrice-weekly administration of buprenorphine (Schottenfeld et al., 2000). Subjects were eligible for the clinical trial if they met FDA criteria for methadone maintenance, had a urine toxicology test positive for opioids, and met DSM-IV criteria for opioid dependence or abuse. The exclusion criteria were the following: (1) current alcohol, sedative, or benzodiazepine dependence; (2) significantly elevated liver function test outcomes (three times the reference range or greater); (3) current psychosis or suicide risk; (4) inability to read or understand rating forms and symptom checklists; and (5) pregnancy. Women of child-bearing age were included provided that they agreed to receive adequate contraception to prevent pregnancy during the course of the study and agreed to have repeat pregnancy tests performed monthly during the study. The study protocol was approved by the human investigations committee of the Yale University School of Medicine, and all subjects provided written informed consent to participate in the study. There were 43 men and 18 women in the sample; the average age of all the subjects was 37.8 years (SD = 7.1 years). Of all the subjects, 57 completed the entire protocol and were included in the analyses; 4 dropped out from the study during the second part of the research protocol after completing the first 2 weeks and were not included in the analyses.

2.2. Medication

The liquid formulation was prepared as a 30% ethanol/water (vol/vol) solution of buprenorphine hydrochloride supplied by the National Institute on Drug Abuse (Research Triangle Institute). Buprenorphine solution was manufactured by the Pharmaceutical Technology Unit of the University of Kentucky (Lexington, KY). Buprenorphine tablets, both active medication and placebo, were manufactured by Reckitt & Colman (UK; now Reckitt–Benckiser).

2.3. Study design

Subjects were randomly assigned to one of three SL buprenorphine dose pairs: (1) 8-mg SL liquid followed by 16-mg SL tablets (n = 18); (2) 12-mg SL liquid followed by 24-mg SL tablets (n = 19); and (3) 16-mg SL liquid followed by 32-mg SL tablets (n = 20). All subjects were first administered with 2 weeks of maintenance with the liquid formulation (8, 12, or 16 mg daily) followed by 2 weeks of maintenance with the corresponding dose (16, 24, or 32 mg daily) of buprenorphine tablets. Buprenorphine was dispensed by an experienced research nurse who also monitored each subject to ensure that doses were held under the tongue for approximately 5 minutes (for the liquid formulation) or until tablets were completely dissolved. The nurse used a wristwatch to measure the duration of holding the medication. Subjects and research staff were kept blind to dose but not to formulation.

Plasma samples from each subject were obtained on two occasions—after at least 10 days of taking the liquid formulation and after at least 10 days of taking the tablet formulation. Because the half-life of buprenorphine reported in the literature varies from 2 to 44 hours, 10 days of maintenance with a given formulation is greater than five times the longest estimate of buprenorphine half-life and, therefore, sufficient to ensure relatively steady-state plasma concentrations (McGettigan, Henry, & Hennesy, 2000). Subjects were medicated between 7 and 9 AM daily. Plasma samples were obtained prior to medication dispensing (0 hour) and then at 1, 2, 4, 6, and 24 hours following administration of the daily buprenorphine dose. At least 3 ml of blood was obtained by an experienced phlebotomist via venipuncture with the use of a vacutainer technique. The samples were then spun for 10 minutes in a centrifuge. Plasma from the tubes was pipetted via a disposable pipette and placed in separate clear tubes labeled with each subject’s code number and the date and time it was drawn. The tubes were then placed in a laboratory freezer at −20°C.
We also obtained daily ratings of opioid withdrawal symptoms with the use of a checklist that included 22 statements (e.g., “My bones and joints are aching” and “I have a runny nose”) rated on a 5-point scale from not at all to extremely. Self-reported illicit opiate and other drug use information were collected weekly using a timeline follow back method, and supervised urine samples were collected three times weekly for toxicology testing using Abbott TDx enzyme assay. Ratings of opioid withdrawal and agonist effects were conducted at each of the plasma collection time points.

2.4. Analysis of blood samples

The plasma samples were shipped on dry ice by overnight courier to the Center for Human Toxicology of the University of Utah (Salt Lake City, UT). The analysis of these specimens was performed using liquid chromatography/tandem mass spectrometry to assess the concentration of buprenorphine in the samples (Moody et al., 2002). All results, with the exception of samples from noncompleters, obtained from this laboratory were used in the statistical analyses.

2.5. Data and statistical analyses

Peak plasma concentrations, areas under the concentration curve (AUCs), and trough concentrations were first analyzed using one-way analysis of variance (ANOVA) separately for the two buprenorphine formulations. Second, the same measures were analyzed using a repeated-measures ANOVA testing for main effects of formulation, time effects, and the interaction. The 24-hour AUCs ($\text{AUC}_{24\ h}$) were calculated using a trapezoid rule using all available data points and without extrapolation to infinity. The bioequivalence was calculated as the ratio of peak, $\text{AUC}_{24\ h}$, and trough concentrations produced by the tablets and the liquid doses, with the tablet results weighted 0.5 to represent the equivalent doses of buprenorphine in both preparations.

3. Results

Administration of increasing doses of buprenorphine liquid (8, 12, and 16 mg) resulted in increased peak plasma concentrations, $F(1, 56) = 13.9, p < .001$, increased $\text{AUC}_{24\ h}$, $F(1, 56) = 8.7, p < .01$, and increased trough plasma levels, $F(1, 56) = 3.4, p = .07$). Pairwise comparisons further showed that the concentrations at 24 hours after the administration of 8 mg were significantly lower than those at 24 hours after the administration of either 12 or 16 mg ($p < .05$) but that the concentrations produced by 12 and 16 mg of liquid buprenorphine at 24 hours after administration did not differ significantly.

Administration of 16 mg of buprenorphine tablets resulted in significantly lower peak, $\text{AUC}_{24\ h}$, and trough plasma concentrations as compared with those from the administration of either 24- or 32-mg tablet doses, but there was no significant difference on any of these measures between the 24- and 32-mg doses. The mean plasma concentrations at six time points, separately for liquid and tablet formulations, are presented in Fig. 1.

Peak concentrations were comparable for 8-mg liquid (3.37 ng/ml) and 16-mg tablet (3.65 ng/ml) but higher for...
24-mg tablet (6.61 ng/ml) as compared with 12-mg liquid (4.53 ng/ml) and for 32-mg tablet (6.22 ng/ml) as compared with 16-mg liquid (5.25 ng/ml). Trough concentrations were approximately twice as high with the tablet doses in each of the three dose pairs (the differences were statistically significant for all dose pairs). AUC$_{24}$ h was also considerably higher with the tablet compared with the liquid dose in all three dose pairs and reached statistical significance for the two higher dose pairs (see Table 1 for details).

The estimated bioequivalence of tablet formulation as compared with liquid ranged from 57% to 75% based on peak concentrations, from 102% to 108% based on trough concentrations, and from 66% to 86% based on AUC$_{24}$ h.

Study participants reported an average of 1 day of heroin use in each week of the study, and 42% of all urine toxicology screens were positive for morphine. There was no statistical difference in self-reported days of heroin use or proportions of opiate-positive urine tests either between the two buprenorphine formulations or among the three dose pairs. No significant correlation between individual buprenorphine plasma concentrations and heroin use was found. Ratings of withdrawal symptoms were also low at all time points, including 24 hours postdosing, and did not correlate with buprenorphine plasma concentrations.

We were also able to calculate the terminal elimination half-life ($t_{1/2}$) from the log-linear regression of plasma concentrations versus the last three time points for all but four sets of data, where one of the three time points was not available. Individual $t_{1/2}$'s varied widely, both between individuals and between sessions; in seven cases, a decrease over time was not observed, resulting in apparent negative $t_{1/2}$'s. The results suggest a trend toward longer $t_{1/2}$'s in the tablet versus liquid formulations. For example, within individuals, a longer $t_{1/2}$ was observed for the tablet formulation for 11 of 15, 14 of 19, and 16 of 19 individuals in the 8/16, 12/24, and 16/32 groups, respectively. Mean values, calculated excluding negative results, and medians were all higher in the tablet phases. Using nonparametric statistics owing to the combination of quantitative and descriptive results, however, we found no significant difference between any of the liquid versus tablet comparison groups.

### Table 1

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$C_{\text{24}}$ (ng/ml)</th>
<th>AUC (ng/ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-mg liquid (n = 18)</td>
<td>3.37 ± 1.29</td>
<td>0.50 ± 0.27</td>
<td>25.4 ± 9.2</td>
</tr>
<tr>
<td>16-mg tablet (n = 18)</td>
<td>3.65 ± 2.35</td>
<td>0.82 ± 0.31$^*$</td>
<td>31.1 ± 14.4</td>
</tr>
<tr>
<td>12-mg liquid (n = 19)</td>
<td>4.53 ± 0.32</td>
<td>0.77 ± 0.09</td>
<td>33.3 ± 11.7</td>
</tr>
<tr>
<td>24-mg tablet (n = 19)</td>
<td>6.61 ± 0.67$^*$</td>
<td>1.58 ± 0.23$^*$</td>
<td>55.7 ± 24.5$^*$</td>
</tr>
<tr>
<td>16-mg liquid (n = 20)</td>
<td>5.25 ± 0.42</td>
<td>0.82 ± 0.14</td>
<td>35.7 ± 11.3</td>
</tr>
<tr>
<td>32-mg tablet (n = 20)</td>
<td>6.22 ± 1.23</td>
<td>1.43 ± 0.18$^*$</td>
<td>54.2 ± 27.9$^*$</td>
</tr>
</tbody>
</table>

Values are expressed as $M ± SEM$.

$^*$ Significantly different from matched liquid formulation by one-way ANOVA ($p < .05$).

4. Discussion

The results of this study indicate that doubling the tablet dose of buprenorphine results in substantially higher trough concentrations and AUC$_{24}$ h and somewhat higher peak plasma buprenorphine concentrations than are obtained with the liquid formulation, especially at higher daily buprenorphine doses. The estimated bioequivalence of tablet doses to liquid doses with regard to peak plasma concentrations ranges from 50% to 75% and that based on AUC$_{24}$ h ranges from 52% to 86%, which are comparable with the results reported previously. These results suggest that buprenorphine doses may need to be increased by 15–45% when converting from liquid to tablet buprenorphine doses to obtain comparable peak buprenorphine plasma levels or average buprenorphine plasma levels over a 24-hour period. However, the range of trough concentrations from 102% to 108% suggests that no adjustment would be needed when converting from liquid to tablet buprenorphine doses to obtain comparable trough plasma levels. Consistent with previous studies, large individual differences in plasma concentrations and no correlation between the concentrations produced by the liquid and tablet doses for the same individuals were found in this study.

The clinical significance of the observed differences in bioequivalence based on peak, trough, or AUC is not known and complicated by the long duration of buprenorphine binding to $\mu$-opioid receptors. If buprenorphine effects on illicit opioid use result from the development of cross-tolerance to opioids or receptor occupancy by buprenorphine and these are related to peak plasma concentrations or sustained plasma concentrations (as represented by the AUC), then increased doses of the tablet formulation might be required to obtain comparable attenuation of blockade and clinical efficacy. The bioequivalence of tablet formulation reached 100% based on trough concentrations, however, suggesting that there might be comparable attenuation of withdrawal symptoms at the same dose of tablet or liquid and, thus, possibly no need for higher tablet doses.

A possible explanation for the differences in the bioequivalence between liquid and tablet formulations when using peak and trough concentrations would be an increase in the $t_{1/2}$ with the tablet formulation. Buprenorphine $t_{1/2}$'s were quite variable; some were even apparently negative, consistent with other studies on SL buprenorphine $t_{1/2}$'s (Kuhlman et al., 1996; Kuhlman, Levine, Johnson, Fudala, & Cone, 1998). The wide variation precluded statistically significant findings, but the trends in group means, medians, and proportion of subjects having longer $t_{1/2}$'s in the tablet session are all consistent with the tablet formulation having a longer $t_{1/2}$: Kuhlman et al. (1996), in discussing differences between the $t_{1/2}$'s of SL and intravenous buprenorphine, suggest the possibility of SL (or buccal) buprenorphine being sequestered into the oral mucosa. Differences in sequestration between the tablet
higher within-subject variability among patients and lower within-subject variability among patients for the two buprenorphine formulations compared to the mono tablet formulation. Although this study was designed as an additional component following the completion of a clinical trial evaluating buprenorphine efficacy for outpatient treatment of heroin dependence (Schottenfeld et al., 2000), the study design was limited to deriving bioequivalence from comparisons of plasma levels between two buprenorphine formulations when one of the formulations contained twice the amount of the studied medication incorporated into different media (liquid vs. tablet) rather than comparing the same doses of two formulations of buprenorphine. Subjects were treated in an outpatient setting, and ongoing illicit drug use, hepatic dysfunction, or use of medications affecting the liver metabolism of some of the subjects may have affected buprenorphine metabolism and, thereby, the determination of accurate trough concentrations and AUC24 h. Urine toxicology testing indicated continuing heroin use in 60% of subjects but no benzodiazepine use during the study. None of the study subjects had significantly elevated results from liver function tests. Data regarding use of other substances or medications are based on self-report and do not indicate that study participants were taking any additional medication that affects buprenorphine metabolism (e.g., antibiotics, analgesics, and carbamazepine) during the study. Because buprenorphine will be used to treat patients in ambulatory settings, however, the study results are applicable to the real world, where some patients may continue illicit drug use. In addition, this study compared the bioequivalence of the mono tablet with that of the liquid formulation and did not evaluate the combination tablet, which is anticipated to be the most widely used formulation in the United States (but not necessarily in other countries). The bioavailability of the combination tablet may be greater than that of the mono tablet (Strain et al., 2004); however, buprenorphine mono tablets are used in many countries outside the United States and may continue to be used in the United States in special circumstances (e.g., with directly observed therapy and with pregnant women).

Overall, the results of this study can be used to provide general guidance in converting buprenorphine dosing regimens established in clinical trials using the liquid formulation for use with the mono tablet formulation.

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References


