Pharmacokinetics and Subjective Effects of Sublingual Buprenorphine, Alone or in Combination with Naloxone
Lack of Dose Proportionality

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Abstract

Objective: Buprenorphine and buprenorphine/naloxone combinations are effective pharmacotherapies for opioid dependence, but doses are considerably greater than analgesic doses. Because dose-related buprenorphine opioid agonist effects may plateau at higher doses, we evaluated the pharmacokinetics and pharmacodynamics of expected therapeutic doses.

Design: The first experiment examined a range of sublingual buprenorphine solution doses with an ascending dose design (n = 12). The second experiment examined a range of doses of sublingual buprenorphine/naloxone tablets along with one dose of buprenorphine alone tablets with a balanced crossover design (n = 8).

Participants: Twenty nondependent, opioid-experienced volunteers.

Methods: Subjects in the solution experiment received sublingual buprenorphine solution in single ascending doses of 4, 8, 16 and 32mg. Subjects in the tablet experiment received sublingual tablets combining buprenorphine 4, 8 and 16mg with naloxone at a 4:1 ratio or buprenorphine 16mg alone, given as single doses. Plasma buprenorphine, norbuprenorphine and naloxone concentrations and pharmacodynamic effects were measured for 48–72 hours after administration.

Results: Buprenorphine concentrations increased with dose, but not proportionally. Dose-adjusted areas under the concentration-time curve for buprenorphine 32mg solution, buprenorphine 16mg tablet and buprenorphine/naloxone 16/4mg tablet were only 54 ± 16%, 70 ± 25% and 72 ± 17%, respectively, of that of the 4mg dose of sublingual solution or tablet. No differences were found between dose strengths for most subjective and physiological effects. Pupil constriction at 48 hours after administration of solution did, however, increase with dose. Subjects reported greater intoxication with the 32mg solution dose, even though acceptability of the 4mg dose was greatest. Naloxone did not change the bioavailability or effects of the buprenorphine 16mg tablet.
Conclusion: Less than dose-proportional increases in plasma buprenorphine concentrations may contribute to the observed plateau for most pharmacodynamic effects as the dose is increased.

Buprenorphine administered sublingually is useful for the treatment of opioid addiction. Doses of 8 mg/day or more are frequently used for maintenance treatment.[1-4] Buprenorphine is administered sublingually because of its extensive first-pass metabolism[5] by liver microsomal cytochrome P450 (CYP) 3A4.[6] Relatively little is known about the pharmacokinetics and pharmacodynamics of buprenorphine given in higher doses, although it is known that the subjective and physiological effects of buprenorphine do not increase in proportion to dose at doses above 4 mg up to 16 mg.[7,8] Although dose-proportional increases in buprenorphine plasma concentrations have been reported with doses up to 32 mg,[7] the immunoassay used in that study did not clearly distinguish buprenorphine from its metabolites.

A combination dose product (Suboxone®[1]) contains naloxone and buprenorphine to decrease diversion to intravenous use. Naloxone (alone) in much larger doses is sufficiently well absorbed sublingually to precipitate withdrawal in opioid-dependent persons, but doses of sublingual naloxone of up to 1–2 mg can be administered without precipitating withdrawal.[9] Naloxone in a ratio of buprenorphine to naloxone of 4:1 when administered intravenously precipitates opioid withdrawal severe enough in dependent users to deter diversion to intravenous use,[10] but has no opioid antagonist effects when administered sublingually at doses used for treatment of opioid dependence.[11-13] The bioavailability of sublingual naloxone in tablet form has yet to be rigorously established, but is probably less than the reported 10–30% from naloxone solutions.[11,14] In contrast, the bioavailability of sublingual buprenorphine from solutions is 30–55%.[11,14-17] The large difference in sublingual bioavailability between buprenorphine and naloxone accounts for the difference in sublingual and intravenous pharmacodynamic effects.

Here we report the results of two experiments examining relationships between buprenorphine and naloxone doses and plasma concentrations and subjective and physiological effects. Buprenorphine and the buprenorphine/naloxone combination doses were in the range of those used for treating opioid dependence. We also attempted to determine the bioavailability of sublingual naloxone. Information on relationships between dose, plasma concentrations and medication effects may aid in optimising dosage.

Methods

Study Design

In the first experiment, buprenorphine was administered by solution given sublingually. In the second, buprenorphine and naloxone combination sublingual tablets were used. Buprenorphine and norbuprenorphine plasma concentrations (and urine concentrations in the tablet study) and subjective and physiological effects were compared between doses.

Subjects were admitted to the General Clinical Research Center ward no later than the evening before each dose and remained until 48 hours following drug administration. They returned at 72 hours for additional measures in the solution study.

Solution Experiment

Twelve subjects received a single dose each of four ascending doses (4, 8, 16 and 32 mg) of sublingual buprenorphine in 1 mL of a 30% ethanol solution. Washout periods were at least 8 days between the 4 and 8 mg doses and at least 10 days between the higher doses.

Tablet Experiment

Eight other subjects received the following four single doses in tablet form approximately 1 week apart in a randomised balanced crossover study with

1 The use of trade names is for product identification purposes only and does not imply endorsement.
the first subject randomised to an order block and each subsequent subject randomised to one of the remaining order blocks: buprenorphine 4mg/naloxone 1mg (B4/N1), buprenorphine 8mg/naloxone 2mg (B8/N2), buprenorphine 16mg/naloxone 4mg (B16/N4), buprenorphine 16mg alone (B16/N0). Buprenorphine 8mg/naloxone 2mg was administered as a single tablet. The other three doses were given as tablets as follows: B4/N1, two tablets of buprenorphine 2mg/naloxone 0.5mg; B16/N4, two tablets of buprenorphine 8mg/naloxone 2mg; B16/N0, two tablets of buprenorphine 8mg. Therefore, the doses were only partially blinded.

Study Population

Healthy volunteers, between the ages of 21 and 45 years and within 15% of ideal body weight for height, were screened by laboratory tests and physical examination to eliminate those with medical illness. All were occasional users of illicit opioids, but not dependent. The women were not pregnant. Subjects were excluded if they had excessive caries, gingivitis or oral infectious or inflammatory disease. Other exclusions were drug dependence (other than on nicotine and caffeine), hypersensitivity to opioids or naloxone, and medication use. Written informed consent was obtained prior to participation. The studies were approved by the Committee on Human Research (IRB), University of California, San Francisco, and carried out in accordance with appropriate ethical guidelines. Subjects were paid for participating.

Buprenorphine and Naloxone Dose Preparation

Buprenorphine solutions were manufactured by the University of Kentucky, Pharmaceutical Technology Unit, Lexington, KY, USA, and the combination tablets by Reckitt and Colman, Hull, UK. Medications were supplied by the National Institute on Drug Abuse. The strength of the tablet was based on the free base content.

Buprenorphine Administration

Subjects provided a sample for urine drug screen on admission. A positive screen for illicit drugs caused postponement of the session or exclusion from the study. Subjects abstained from smoking and eating for 1 hour before drug administration and did not eat, drink or smoke for 1 hour after. The buprenorphine dose in a 1mL solution or the combination tablet(s) were placed under the tongue. Subjects were asked not to swallow for 5 minutes after administration for the solution experiment. For the tablet experiment, they were instructed not to swallow until the tablet had disintegrated. The sublingual area was examined for tablet fragments at 5 minutes after administration. If fragments remained, the subject was asked not to swallow until the tablet(s) were completely dissolved (i.e. the subject could no longer detect the fragments) or until 10 minutes following administration, whichever occurred first. The time of any premature swallows was recorded.

Biological Fluid Sampling

Blood samples (7mL per sample) were obtained through an intravenous catheter immediately before administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48 and 72 hours after for the solution experiment and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36 and 48 hours after drug administration for the tablet study. Samples were immediately cooled and plasma was separated by centrifugation within 30 minutes of blood collection. Samples were stored at −20°C until assayed.

In the tablet experiment only, urine was collected for 48 hours after administration. Urine was stored at −20°C until assayed.

Measurement of Plasma and Urine Buprenorphine

Plasma and urine concentrations of buprenorphine, norbuprenorphine and naloxone were determined by a liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method. Samples were analysed with a PE Sciex API III system monitored with LC/MS/MS in multiple reaction monitoring mode. In plasma, the lower limit of quantification was 0.050 µg/L for buprenorphine, norbuprenorphine and naloxone. Interday precision analysis used 12 samples for each of four concentrations in six separate runs. Intraday precision analysis used six samples for each of four concentrations. For the solution experiment, calibra-
tion curves were linear from 0.05 to 0.2 µg/L. Coefficient of variation (CV) ranged from 3.48 to 12.0% for plasma buprenorphine. The relative error (RE) ranged from −0.0175 to +4.37%. Accuracy and precision of spiked control samples at 0.2, 0.4, 1, 6 and 15 µg/L, assayed concurrently with study samples, showed a CV ranging from 5.14 to 10.1% and an RE ranging from −1.13 to +3.82%. Interday precision and accuracy CV ranged from 5.85 to 9.94% for norbuprenorphine and from 6.62 to 8.36% for naloxone. The RE ranged from 0 to 7.25% for norbuprenorphine and from −2.67 to +7.87% for naloxone. Intraday CVs ranged from 3.29 to 7.27% for norbuprenorphine and from 3.50 to 7.70% for naloxone, and REs from −8.67 to +7.87% for norbuprenorphine and from −3.33 to +11.0% for naloxone.

For the tablet experiment, coefficients of variation for the interday precision analysis of 12 samples for each of the four concentrations in six separate runs ranged from 5.19 to 6.45% for buprenorphine, from 5.85 to 9.94% for norbuprenorphine, and from 6.62 to 8.36% for naloxone. RE ranged from −2.67 to +9.13% for buprenorphine, from 0 to 7.25% for norbuprenorphine, and from −2.67 to +7.87% for naloxone. In intraday precision analysis of six samples for each of the four concentrations, CVs ranged from 1.42 to 3.22% and REs ranged from −2.67 to +12.0% for buprenorphine. CVs ranged from 3.29 to 7.27% and REs ranged from −8.67 to +7.87% for norbuprenorphine. CVs ranged from 3.50 to 7.70%, and REs ranged from −3.33 to +11.0% for naloxone.

In urine (tablet experiment only), the lower limit of quantification was 0.2 µg/L for buprenorphine and naloxone and 0.5 µg/L for norbuprenorphine. In interday precision analysis, CVs ranged from 2.25 to 6.59% for buprenorphine, from 4.01 to 7.32% for norbuprenorphine, and from 4.54 to 5.68% for naloxone. REs ranged from +2.57 to +9.56% for buprenorphine, from +0.59 to +12.2% for norbuprenorphine, and from +3.61 to +9.74% for naloxone. In intraday precision analysis, CVs ranged from 1.92 to 7.45% for buprenorphine, from 3.69 to 9.23% for norbuprenorphine, and from 3.01 to 5.27% for naloxone. REs ranged from −5.81 to +3.11% for buprenorphine, from −3.45 to +8.14% for norbuprenorphine, and from −1.57 to +4.12% for naloxone.

Physiological Measures

Heart rate, blood pressure, and pulse oximetry were measured with a cardiovascular monitor (VSM 2; Physio Control, Redmond, WA, USA) prior to administration and at approximately the same times as blood collections. Rate pressure product was calculated as the product of heart rate and systolic blood pressure. Respiratory rate was measured by counting inhalations per minute. Pupil diameter was measured on the horizontal axis from photographs taken under consistent light and eye fixation conditions with a Polaroid CU-5 Land Camera with lens adjusted for close-up photography. A reference photo of the eye and ruler was used to convert measured values to actual mm units. Measurements were taken predose and at 1, 3, 6 and 48 hours after administration for the solution study and at 1, 3 and 6 hours for the tablet study. Saliva pH was measured (Accumet 1001 hand-held pH meter; Fisher Scientific, Pittsburgh, PA, USA) just before drug administration in both experiments and again immediately after swallowing following sublingual dissolution of the tablet.

Subjective Measures

Subjective symptom reports were obtained from subjects before administration, at frequent intervals for the first 6 hours, and at 24 and 48 hours after administration. Subjects were asked to estimate intensity of global intoxication and opioid withdrawal by verbally reporting a number between 0 and 100, where 0 was no effect and 100 the maximum effect.

Good drug effect, bad drug effect, drug liking and sickness were rated with a visual analogue scale by marking along a 10cm line from 0 (not at all) to 100 (extreme).

The ‘Opiate Agonist Scale’ contains 16 opioid agonist effect items. Intensity of each item was rated from 0 to 4, with 0 as no effect and 4 as maximum effect for a maximum total score of 64.

The ‘Opiate Withdrawal Scale’ (tablet experiment only) consisted of 21 typical opioid antagonist symptoms. Intensity of each item was rated from 0 to 4 with 0 as no effect and 4 as maximum effect for a maximum total score of 84.

Subjects were asked to report any other effects or symptoms and whether the drug they received...
would be acceptable to them as a medication. Researchers recorded vomiting episodes and amounts and other objective ill effects during the 6-hour observation period, asked about problems or ‘bad effects’ from the drug the morning following administration, and reviewed chart nursing notes for adverse effects.

Subjective reports were collected using paper and pencil for the solution experiment and with a computer for the combination tablet experiment.

**Statistical Analysis**

**Pharmacokinetic Measures**

The following pharmacokinetic parameters were estimated for buprenorphine from plasma concentration-time profiles using standard noncompartmental methods: area under the plasma concentration-time curve (AUC) to 72 hours for the solution experiment and 48 hours for the tablet experiment (AUC\(_{72}\) and AUC\(_{48}\)), peak plasma concentrations (C\(_{\text{max}}\)) and peak times (t\(_{\text{max}}\)). AUC was determined using the trapezoidal method for periods of increasing or stationary concentration and the logarithmic-trapezoidal method for periods of decreasing concentration to the last measured plasma concentration for unextrapolated AUCs.

All pharmacokinetic parameters were statistically analysed as their logarithmic (natural) transforms, except peak time, which was analysed untransformed. All parameters, except peak time, were analysed per drug dose with dose correction made before the logarithmic transformation. Pharmacokinetic parameters were compared between treatments using linear regression and analysis of variance (ANOVA). If a significant test was found, then further comparison between treatments used a Tukey multiple comparison procedure.

**Physiological and Subjective Measures**

Physiological and subjective effects were analysed by repeated-measures ANOVA with treatment as the within-subject factor. Postdose values in each condition were compared with baseline values and with one another. Values were converted into change scores by subtracting baseline values from postdrug values. Change scores were analysed by ANOVA. Following a significant test, pairwise comparisons were performed using the least squares means analysis. Effects were considered significant at \( p \leq 0.05 \). Data were adjusted for sphericity using the Huynh-Feldt adjustment factor. Huynh-Feldt corrected significance values are reported (SuperANOVA, Macintosh, Berkeley, CA, USA).

**Results**

**Study Population**

Ten men and two women (aged 23–34 years) took part in the solution experiment. Most typically used 0.125–0.5g of heroin per occasion. Seven men and one woman in the combination tablet experiment (aged 22–42 years) reported similar use. Mean bodyweight was not statistically significantly different between experiments.

**Salivary pH and Tablet Dissolution Time**

No significant difference was found in salivary pH between conditions (table I). Mean ± SD dissolution times for the tablet study were 4 ± 1, 7 ± 2, 8 ± 1 and 7 ± 1 minutes for the 4mg, 8mg and 16mg buprenorphine combination tablets, and the 16mg buprenorphine alone tablets, respectively. Tablet dissolution time was significantly shorter with the

<table>
<thead>
<tr>
<th>Table I. Salivary pH</th>
<th>Condition</th>
<th>Salivary pH (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solution experiment (predose only)</strong></td>
<td>Buprenorphine 4mg</td>
<td>6.9 ± 0.4</td>
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<tr>
<td></td>
<td>Buprenorphine 8mg</td>
<td>6.7 ± 0.4</td>
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<tr>
<td></td>
<td>Buprenorphine 16mg</td>
<td>6.7 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine 32mg</td>
<td>6.9 ± 0.4</td>
</tr>
<tr>
<td><strong>Tablet experiment</strong></td>
<td>Buprenorphine 4mg/haloxone 1mg</td>
<td>6.9 ± 0.6</td>
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<tr>
<td></td>
<td>predose</td>
<td>6.4 ± 0.6</td>
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<tr>
<td></td>
<td>postdose</td>
<td>6.5 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine 8mg/haloxone 2mg</td>
<td>6.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>predose</td>
<td>6.5 ± 0.5</td>
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<tr>
<td></td>
<td>postdose</td>
<td>6.3 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine 16mg/haloxone 4mg</td>
<td>6.7 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>predose</td>
<td>6.3 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>postdose</td>
<td>6.4 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine 16mg alone</td>
<td>6.9 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>predose</td>
<td>6.4 ± 0.3</td>
</tr>
</tbody>
</table>
4mg buprenorphine/naloxone tablet than with the other tablets (p < 0.05). Dissolution times were not significantly different between the other dose conditions. Tablet dissolution time was not significantly correlated with post-treatment saliva pH. Of the eight subjects given tablets, two frequently swallowed prematurely. One had typical buprenorphine concentrations. For the other, plasma concentrations were lower than the group mean but did not meet the outlier criterion of two standard deviations from the mean and were no lower than the values of some of the other subjects, so data were included in the analysis. One subject in the solution study swallowed prematurely at 1 minute 40 seconds after the 4mg dose. His data were similar to those of the other subjects at this dose and were included in the analysis.

Pharmacokinetic Measures

Figure 1 illustrates the time course of buprenorphine and norbuprenorphine plasma concentrations. Derived pharmacokinetic values are in table II, including dose-corrected mean AUC and Cmax values. Extrapolated AUC values (AUC∞) were not compared because we could not characterise the terminal slope for several of the concentration-time curves due to fluctuating terminal values. This difficulty also precluded calculation of valid half-lives.

Solution Experiment

The tmax for the solution did not differ with dose (not dose-adjusted). However, a consistent trend for lower relative values with each increase in dose was noted for dose-adjusted AUC72 and Cmax, confirmed by statistically significant contrasts for linear trend output by the ANOVA (p = 0.0001, and p = 0.0001, respectively). AUC72 per mg of dose administered after the 4mg and 8mg doses did not differ, but the dose-corrected AUC72 for the 16mg dose was only 72 ± 14%, and for the 32mg dose only 54 ± 16%, of that of the 4mg dose. Per mg dose administered, the 8, 16 and 32mg doses yielded only 84 ± 23%, 63 ± 19% and 52 ± 16%, respectively, of the Cmax of the 4mg dose.

Tablet Experiment

Similarly, mean buprenorphine AUC48 and mean Cmax also increased, but less than proportionally, with the dose of buprenorphine in the tablet study. The highest buprenorphine dose (16mg), whether alone or in combination with naloxone 4mg, generated a lower AUC48 for each of buprenorphine and norbuprenorphine per mg of dose than did the lowest buprenorphine dose (buprenorphine 4mg/naloxone 1mg). Per mg of dose, buprenorphine AUC48 from buprenorphine 16mg alone and in combination with naloxone was only 70 ± 25% and 72 ± 17%, respectively, of that from the buprenorphine 4mg combination dose. Comparing the 16mg tablet of buprenorphine alone to the 16mg solution, the tablet yielded 72% of the AUC48 and 65% of the Cmax of that of the solution. However, the 24-hour buprenorphine concentrations were not significantly different. Norbuprenorphine plasma concentrations at later collection times were relatively higher than those of buprenorphine, yielding a larger AUC48. Compared with the same buprenorphine dose conditions in the solution study, the ratios of norbuprenorphine to buprenorphine AUC48 were larger for the 4, 8 and both 16mg doses (with and without naloxone) in the tablet study (p < 0.05, 0.01, 0.01 and 0.01, respectively).

So many naloxone concentrations were below the level of detection that comparisons between dose conditions could not be made. Only five of the eight subjects had more than two plasma concentrations of naloxone above the detection threshold at the highest dose. The highest AUC was only 0.55 µg • h/L.

Naloxone did not alter the bioavailability of buprenorphine from the 16mg buprenorphine tablet as assessed by comparisons of the buprenorphine AUC48 (i.e. buprenorphine 16mg/naloxone 4mg tablet versus buprenorphine 16mg alone tablet). However, naloxone did increase (p < 0.05) the buprenorphine concentration at 24 hours after administration with the buprenorphine 16mg tablet by 34% (from 0.387 ± 0.19 to 0.519 ± 0.16 µg/L).

Only a small percentage of the buprenorphine dose was excreted unchanged in the 48-hour urine collection. The total of buprenorphine and norbuprenorphine and their hydrolysable conjugates was only 4.1 ± 1.6–5.7 ± 2.2%.
Physiological Effects

Heart rate, blood pressure, rate-pressure product, respiratory rate and pulse oximetry were not significantly different between doses in either experiment. However, at 48 hours after solution doses, pupils were still constricted, with larger doses producing greater constriction. A dose-response effect was found at this time (p < 0.01). The pupil constriction after the 32mg dose was greater than with the 4mg dose (t = 2.87, p < 0.01) [figure 2]. Pupil diameter in the tablet study was not significantly different between conditions but was not measured at 48 hours.
Table II. Plasma pharmacokinetics of buprenorphine and norbuprenorphine after sublingual doses of buprenorphine and/or naloxone. Values are means ± SD (n = 12 for solution doses and n = 8 for tablet doses)

<table>
<thead>
<tr>
<th>Doses (mg)</th>
<th>Dose-adjusted AUC (µg • h/L per mg)</th>
<th>Unadjusted AUC (µg • h/L)</th>
<th>Dose-adjusted Cmax (µg/L)</th>
<th>Unadjusted Cmax (µg/L)</th>
<th>Unadjusted tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td></td>
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<tr>
<td>Sublingual solution</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>B4</td>
<td>4.34 ± 1.36</td>
<td>17.36 ± 5.44</td>
<td>0.890 ± 0.378</td>
<td>3.56 ± 1.51</td>
<td>1.09 ± 0.40</td>
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<tr>
<td>B8</td>
<td>3.84 ± 1.23</td>
<td>30.70 ± 9.86</td>
<td>0.729 ± 0.346</td>
<td>5.83 ± 2.77</td>
<td>1.16 ± 0.54</td>
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<tr>
<td>B16</td>
<td>3.02 ± 0.86</td>
<td>48.26 ± 13.72</td>
<td>0.523 ± 0.179</td>
<td>8.37 ± 2.86</td>
<td>1.17 ± 0.40</td>
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<tr>
<td>B32</td>
<td>2.20 ± 0.50</td>
<td>70.30 ± 15.86</td>
<td>0.428 ± 0.137</td>
<td>13.70 ± 4.38</td>
<td>1.00 ± 0.34</td>
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<td>p-Value</td>
<td>p = 0.0001 (B32 &lt; B16 &lt; B4) and B16 &lt; B8 &lt; B4</td>
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<td>Sublingual tablet</td>
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<tr>
<td>B4/N1</td>
<td>3.13 ± 1.09</td>
<td>12.52 ± 4.37</td>
<td>0.460 ± 0.180</td>
<td>1.84 ± 0.72</td>
<td>1.06 ± 0.42</td>
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<td>B8/N2</td>
<td>2.53 ± 1.09</td>
<td>20.22 ± 8.70</td>
<td>0.375 ± 0.191</td>
<td>3.00 ± 1.53</td>
<td>1.01 ± 0.36</td>
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<tr>
<td>B16/N4</td>
<td>2.18 ± 0.73</td>
<td>34.89 ± 11.63</td>
<td>0.372 ± 0.143</td>
<td>5.95 ± 2.28</td>
<td>0.79 ± 0.27</td>
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<td>B16/N0</td>
<td>2.04 ± 0.51</td>
<td>32.63 ± 8.23</td>
<td>0.342 ± 0.079</td>
<td>5.47 ± 1.27</td>
<td>1.04 ± 0.65</td>
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<td>p-Value</td>
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<td>Norbuprenorphine</td>
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<td>Sublingual solution</td>
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<tr>
<td>B4</td>
<td>1.86 ± 0.98</td>
<td>7.44 ± 3.92</td>
<td>0.083 ± 0.042</td>
<td>0.33 ± 0.17</td>
<td>3.92 ± 8.27</td>
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<tr>
<td>B8</td>
<td>2.06 ± 0.93</td>
<td>16.49 ± 7.40</td>
<td>0.111 ± 0.042</td>
<td>0.88 ± 0.34</td>
<td>2.96 ± 3.06</td>
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<tr>
<td>B16</td>
<td>1.79 ± 0.96</td>
<td>28.62 ± 15.38</td>
<td>0.077 ± 0.055</td>
<td>1.24 ± 0.87</td>
<td>2.75 ± 2.65</td>
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<td>B32</td>
<td>1.55 ± 0.95</td>
<td>49.59 ± 30.33</td>
<td>0.077 ± 0.054</td>
<td>2.48 ± 1.74</td>
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<td>p-Value</td>
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<td>Sublingual tablet</td>
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<tr>
<td>B4/N1</td>
<td>3.81 ± 1.53</td>
<td>15.24 ± 6.13</td>
<td>0.208 ± 0.068</td>
<td>0.83 ± 0.27</td>
<td>4.81 ± 8.00</td>
</tr>
<tr>
<td>B8/N2</td>
<td>2.90 ± 0.97</td>
<td>23.16 ± 7.78</td>
<td>0.185 ± 0.070</td>
<td>1.48 ± 0.56</td>
<td>1.07 ± 0.48</td>
</tr>
<tr>
<td>B16/N4</td>
<td>2.54 ± 1.16</td>
<td>40.62 ± 18.49</td>
<td>0.219 ± 0.087</td>
<td>3.50 ± 1.39</td>
<td>0.98 ± 0.42</td>
</tr>
<tr>
<td>B16/N0</td>
<td>2.04 ± 0.48</td>
<td>32.64 ± 7.63</td>
<td>0.159 ± 0.081</td>
<td>2.54 ± 1.29</td>
<td>1.44 ± 0.86</td>
</tr>
<tr>
<td>p-Value</td>
<td>p = 0.0026 (B16/N4 &lt; B4/N1; B16/N0 &lt; B4/N1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subjective Measures

Larger doses of solution, but not larger doses of tablet, produced increased global intoxication. Global intoxication in the solution experiment was rated significantly higher following administration of the 32mg sublingual solution than after the 4 and 8mg doses (t = −2.85, p < 0.01), but not compared with the 16mg dose. Intoxication appeared within 30 minutes after administration, peaked at approximately 120 minutes and remained moderately high to the end of the 6-hour testing session, and was back to baseline by 24 hours.

Compared with baseline, ratings of drug liking and good drug effect increased in all conditions. However, compared across conditions in the solution experiment, drug liking was significantly higher across time in the 4mg condition than after the 8, 16 and 32mg doses (t = 2.15, p < 0.04; t = 2.15, p < 0.04; and t = 3.01, p < 0.01, respectively) and remained high to the end of the 6-hour session. Drug

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liking for the tablet increased with increasing dose, but this was not statistically significant. Good drug effect and opioid agonist ratings were not different between the solution or tablet conditions. Peak ratings for global intoxication and drug liking are shown in figure 3.

For both experiments, unpleasant effects were small and statistically nonsignificant. Global withdrawal effects peak means were ≤ 8 (out of a possible maximum of 100), opioid withdrawal symptoms peak means ≤ 5 (out of 84), and ratings of sickness and bad drug effect peak means ≤ 18 (out of 100) with any dose of the solution or tablets.

**Subject Comments**

Acceptability of the buprenorphine solution as an opioid-like medication was 68% for the 4mg dose, 25% for the 8mg dose, and 33% for the 16 and 32mg doses. Similarly, acceptability was highest (88%) for the buprenorphine 4mg/naloxone 1mg tablet and lowest (50%) for the buprenorphine 16mg tablet.

**Adverse Effects**

In the solution experiment, nausea or vomiting was reported by 9 of the 12 subjects. Vomiting was more frequent after increased dose. Difficulty urinating (hesitancy or brief, spontaneously resolving retention over the course of the evening following administration) was reported by half of the subjects. In the tablet study, 3 of the 12 subjects vomited. Vomiting was unrelated to dose.

**Discussion**

**Pharmacokinetic Measures**

AUC for buprenorphine in both experiments increased with dose but less than proportionally. Several subjects vomited in both experiments. This raises the question of whether vomiting contributed to the lack of dose proportionality. It is possible that if a large proportion of the buprenorphine dose were swallowed, vomiting might explain this finding. However, vomiting was related to increasing dose only in the solution experiment and very little buprenorphine is available after oral doses. Therefore, loss of buprenorphine from vomiting would be unlikely to significantly alter plasma concentrations.

Differences in dose-corrected AUC could reflect a difference either in bioavailability or in clearance. The randomised dose order in the tablet experiment makes induction of enzymes producing faster clearance a less likely explanation. The proportionately decreasing AUC of a major metabolite, norbuprenorphine, with increasing buprenorphine dose is also more consistent with decreased sublingual absorption, rather than a change in elimination. Tablet dissolution for the 4mg buprenorphine/naloxone dose was shorter than for the others, allowing less time for swallowing which, in turn, could result in poorer absorption from the stomach and intestines for the larger doses compared with the smaller. The higher norbuprenorphine to buprenorphine ratios in the tablet study compared with the solution study suggests that more of the tablet may be swallowed, as proportionately increased norbuprenorphine concentrations are found with oral administration. Although larger doses may simply be more difficult to mechanically hold under the tongue, resulting in more drug swallowed before absorption, it is also possible that larger doses may saturate the tissue transporter mechanisms, increasing sequestration of buprenorphine in sublingual tissues. Drug that is not moving through sublingual tissues may be swallowed and cleared by CYP3A4 in the liver or by the
hepatobiliary system. Faecal excretion accounts for more than 74% of the elimination of buprenorphine and norbuprenorphine, based on animal and autopsy studies. The low, approximately 5%, recovery of buprenorphine, norbuprenorphine and their hydrolysable conjugates in the urine in our study is consistent with most of the drug being excreted through other routes, presumably in faeces.

The relatively long time for peak concentration at about 1 hour after dose could be explained by several possible mechanisms. These include a saturation of a transport process facilitating absorption; a sequestration of buprenorphine in the oral mucosal or other tissues; and a slower absorption from gut after swallowing if a greater than expected proportion was swallowed. However, this last explanation is unlikely since the small amount absorbed from gut would not account for the shift in $t_{\text{max}}$.

The lower availability from the tablet than from solution is consistent with the 50–64% found in other studies. However, the 24-hour plasma concentration (a trough concentration if administered daily) after the tablet and the solution were not different, consistent with earlier findings.

Dose-proportional increases in buprenorphine plasma concentrations reported by Walsh et al. contrast with our findings of decreasing bioavailability with increasing dose. Their use of a less specific radioimmunoassay that may have cross-reacted with buprenorphine and its metabolites, yielding higher concentrations of ‘buprenorphine equivalents’ in the higher dose conditions, may account for the different findings. Unless the metabolites are biologically active, incomplete dose-proportionality of buprenorphine concentrations would be expected to produce less than dose-proportional effects.

Very little naloxone was absorbed sublingually from the combination dose tablet, consistent with earlier findings of the relatively lower amounts about 1 hour after dose could be explained by several possible mechanisms.

Physiological and Subjective Effects

Naloxone did not produce opioid withdrawal effects or diminish the reported pleasurable effects of buprenorphine.

Pupils were more constricted after the 32mg dose of the solution at 48 hours after administration and participants reported higher ratings of global intoxication with the 32mg solution dose, even though acceptability of the 4mg dose of buprenorphine was greatest for both solution and tablet. However, dose did not alter most subjective and physiological vari-
ables in the 4–16 and 4–32mg dose comparisons. Although small sample size may have been a factor, the lack of a graded response for many effects over the administration range suggests that our lowest dose, 4mg, may have been producing a plateau for these effects in our nondependent subjects. The less than dose-proportional increases in plasma concentration with increasing dose may contribute to this finding. However, intravenous doses of buprenorphine 0–16mg added to sublingual buprenorphine 12mg did not produce different effects for most cardiorespiratory measures. So, the ceiling for some pharmacodynamic effects may be independent of dose within the range commonly used for treatment of opioid dependence.

The $t_{\text{max}}$ of 1 hour and peak time of subjective effects at 2 hours with lasting effects is consistent with the slow receptor association, high affinity and slow receptor dissociation found for buprenorphine. If buprenorphine sequestrates in the central nervous system and saturates receptors at the typically much lower doses used for pain relief, the high affinity and slow dissociation could also explain the plateau in subjective effects with higher doses.

**Conclusions**

Sublingual buprenorphine as solutions (4–32mg) or in tablet form (4–16mg) combined with naloxone showed an increase in AUC with dose that was less than proportional. All doses produced similar subjective and physiological effects, consistent with the apparent decrease in bioavailability with increasing dose. However, a lack of dose-related response suggests that a balance of pleasurable and unpleasant effects or a plateau effect at 4mg may have played a role. Reassessment in opioid-dependent people would be necessary to confirm that the same plateau in effects applies to that target treatment population. Decreasing bioavailability and plateau effect suggest greater safety at larger doses or in overdose situations. The addition of naloxone to buprenorphine to discourage diversion to parenteral use was well tolerated, suggesting that the combination tablet will be a useful option for maintenance treatment.

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**References**


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