ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2004; 43 (5): 329-340
0312-5963/04/0005-0329/$31.00/0

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 β 16%, 70 β 25% and 72 β 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 4mg up to 16mg.[7,8] Although dose-proportional increases in buprenorphine plasma concentrations have been reported with doses up to 32mg,[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 1–2mg 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 32mg) of sublingual buprenorphine in 1mL of a 30% ethanol solution. Washout periods were at least 8 days between the 4 and 8mg 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 bodyweight 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 −20τC until assayed.

In the tablet experiment only, urine was collected for 48 hours after administration. Urine was stored at −20τC 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.[18] 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 • g/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 • g/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 • g/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 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 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 • g/L for buprenorphine and naloxone and 0.5 • g/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.[19] 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.[19] 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_{max}) and peak times (t_{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 β SD dissolution times for the tablet study were 4 β 1, 7 β 2, 8 β 1 and 7 β 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 I. Salivary pH

Condition	Salivary pH (mean β SD)
Solution experiment (predose only)	
Buprenorphine 4mg	6.9 β 0.4
Buprenorphine 8mg	6.7 β 0.4
Buprenorphine 16mg	6.7 β 0.4
Buprenorphine 32mg	6.9 β 0.4
Tablet experiment	
Buprenorphine 4mg/naloxone 1mg	
predose	6.9 β 0.6
postdose	6.4 β 0.4
Buprenorphine 8mg/naloxone 2mg	
predose	6.8 β 0.6
postdose	6.5 β 0.5
Buprenorphine 16mg/naloxone 4mg	
predose	6.7 β 0.4
postdose	6.3 β 0.5
Buprenorphine 16mg alone	
predose	6.9 β 0.7
postdose	6.4 β 0.3

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