Human Pharmacokinetics of Intravenous, Sublingual, and Buccal Buprenorphine*

James J. Kuhlman, Jr.[1], Shairose Lalani[1], Joseph Magluilo, Jr.[1], Barry Levine[1], William D. Darwin[2], Rolley E. Johnson[2,†], and Edward J. Cone[2]

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Abstract

Buprenorphine is a potent opioid analgesic used in the treatment of moderate to severe pain. At higher doses, it has demonstrated potential for treating heroin dependence. This study was undertaken to investigate buprenorphine pharmacokinetics by different routes of administration at dosages approximating those used in opioid-dependence studies. Six healthy men who were nondependent but who had a history of heroin use were administered buprenorphine in a crossover design study by intravenous (1.2 mg), sublingual (4.0 mg), and buccal (4.0 mg) routes of administration. Plasma samples were collected up to 96 h and assayed for buprenorphine and norbuprenorphine by negative chemical ionization tandem mass spectrometry. Plasma concentrations of buprenorphine and norbuprenorphine were analyzed by nonlinear regression analysis with standard noncompartmental methods. Buprenorphine bioavailability by the sublingual and buccal routes was estimated as 51.4% and 27.8%, respectively, although there was considerable interindividual variability by both routes of administration. The terminal elimination half-lives were longer for the sublingual and buccal routes than for the intravenous route. The extended elimination half-lives may be due to a shallow depot effect involving sequestration of buprenorphine in the oral mucosa. Norbuprenorphine mean peak plasma concentrations were less than 1 ng/mL and were highly variable among different routes of administration and individuals. The terminal elimination half-life of norbuprenorphine was longer than buprenorphine.

Introduction

Buprenorphine is a semisynthetic opioid used for the treatment of moderate to severe pain in postoperative and cancer cases. Therapeutic doses administered by the intravenous and intramuscular routes range from 0.3 to 0.6 mg. Buprenorphine produces effects similar to morphine but is 25–40 times more potent and has a large therapeutic index. At higher doses (4–16 mg), buprenorphine has been shown to be an effective treatment for suppressing heroin withdrawal (1). Buprenorphine appears to display a ceiling effect at high doses and has been categorized as a partial agonist at the μ receptor. Walsh et al. (2) found that buprenorphine produced less respiratory depression at a 32-mg sublingual dose than at a 16-mg dose. Buprenorphine also possesses an unusually long duration of action most likely due to its high affinity for opioid receptors.

Jasinski et al. (3) suggested in 1978 that buprenorphine may be useful in the treatment of opioid-dependent individuals because it produced morphine-like subjective effects, had a long duration of action, and produced limited withdrawal symptoms. Mello and co-workers (4,5) demonstrated that buprenorphine significantly suppressed heroin self-administration. A daily subcutaneous dose of 4–8 mg of buprenorphine reduced heroin self-administration of experienced heroin abusers by 69–98%.

A nonparenteral dosage form of buprenorphine that could achieve and maintain blood levels that prevent opiate craving and withdrawal would be preferred for the treatment of opioid-dependent individuals. Buprenorphine, unlike methadone, is less effective by the oral route of administration and undergoes a significant first-pass effect. The bioavailability of an oral dose of buprenorphine was estimated as 15% (6). Consequently, oral buprenorphine treatment requires large relative doses, which increase the cost to a prohibitive level. The sublingual route exhibits greater bioavailability and has been used extensively in clinical efficacy studies (7–11). Other routes of administration, such as the buccal route, could also be effective means of drug delivery of buprenorphine.

An understanding of buprenorphine pharmacokinetics by different routes of administration is essential for determining the most efficient treatment of opioid dependence. A number of studies reported pharmacokinetic data for buprenorphine administered at lower analgesic doses by the intravenous (12–15), intramuscular (12), and sublingual (6,16,17) routes. Buprenorphine elimination half-lives ranged from 3 to 5 h, and

* Disclaimer: The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of Defense or of the Army, Navy, or Air Force.

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was considerable interindividual variability (6). No pharmacokinetic information is available for norbuprenorphine, the active metabolite of buprenorphine, in humans. Much of the buprenorphine pharmacokinetic data has been obtained with radioimmunoassay. Unfortunately, cross-reactivity with buprenorphine glucuronide and norbuprenorphine makes these data less reliable. We developed a specific gas chromatographic–tandem mass spectrometric (GC–MS–MS) assay for buprenorphine and norbuprenorphine in biological fluids (18). The assay was used for the measurement of these analytes in the plasma of six individuals after intravenous, sublingual, and buccal administration. The buprenorphine doses administered approximated those used in opioid-dependence studies. Pharmacokinetic parameters and estimates of bioavailability for the sublingual and buccal routes of administration are reported.

Methods

Chemicals and materials

Buprenorphine HCl and norcodeine were purchased from Sigma Chemical Co. (St. Louis, MO). Buprenorphine-d_4 and buprenorphine were purchased from Radian Corp. (Austin, TX). Buprenorphine from separate sources was used to prepare calibrator and control samples. Norbuprenorphine was obtained from the Research Technology Branch, National Institute on Drug Abuse (Rockville, MD). Heptafluorobutyric anhydride (HFBA) was purchased from Aldrich Chemical Co. (Milwaukee, WI). All solvents were obtained from Fisher Chemical (Fair Lawn, NJ) and were high-performance liquid chromatographic-grade. Clean Screen (ZCDAU020) solid-phase extraction columns were purchased from World Wide Monitoring (Bristol, PA). Argon and ammonia gases from MG Industries (Valley Forge, PA) were used in chemical ionization tandem mass spectrometry.

Instrumentation

Quantitative analyses were performed with a Finnigan MAT TSQ 700 tandem mass spectrometer equipped with a Varian 3400 gas chromatograph. Injections were made by a split–splitless injector onto a J&W DB-5 MS capillary column (15 m × 0.25-mm i.d.,

Table I. Plasma Concentrations of Buprenorphine and Norbuprenorphine after Buprenorphine Administration by the Intravenous, Sublingual, and Buccal Routes of Drug Administration

Time (h)	Subject plasma concentrations (ng/mL)						Mean	SEM
	A	C	D	E	G	I		
1.2-mg buprenorphine–intravenous								
–0.50	0	0	M†	0	0	0	0	0
0.04	37.83	43.93	M	25.60	24.40	55.83	37.52	5.88
0.08	16.71	26.21	M	13.43	12.40	28.24	19.40	3.29
0.13	12.85	15.81	M	11.10	11.10	18.07	13.79	1.37
0.17	9.53	18.92	M	7.71	7.03	13.64	11.37	2.21
0.25	6.92	10.82	M	5.00	5.25	M	7.00	1.34
0.33	5.52	11.01	M	3.75	4.19	7.84	6.46	1.34
0.50	4.27	7.81	M	3.00	3.07	6.44	4.92	0.95
0.75	3.64	6.37	M	2.03	2.76	5.97	4.15	0.86
1.00	2.69	4.90	M	1.05	2.16	4.67	3.09	0.74
1.50	1.71	3.90	M	0.88	1.79	4.07	2.47	0.64
2.00	0.87	2.46	M	2.05	1.32	2.50	1.84	0.32
3.00	1.04	1.92	M	1.22	0.77	1.76	1.34	0.22
4.00	0.43	1.06	M	0.90	0.56	1.05	0.80	0.13
5.00	0.33	0.61	M	0.54	0.22	0.57	0.45	0.08
6.00	0.28	0.87	M	0.55	0.18	0.49	0.47	0.12
7.00	0.25	0.67	M	1.01	0.21	0.51	0.53	0.15
10.00	0.26	0.21	M	0.38	M	0.43	0.32	0.05
13.00	0	0	M	0.40	0.17	0.26	0.17	0.08
23.75	0	0	M	0.18	0	0	0.04	0.04
28.00	0	0	M	0.19	0	0	0.04	0.04
36.00	0	0	M	0.21	0	0	0.04	0.04
48.00	0	0	M	0	0	0	0	0
60.00	0	0	M	0	0	0	0	0
72.00	0	0	M	0	0	0	0	0
96.00	0	0	M	0	0	0	0	0
1.2-mg norbuprenorphine–intravenous								
–0.50	0	0	0	0	0	0	0	0
0.04	0.18	0.18	0.25	0	0.10	0.81	0.25	0.12
0.08	0.13	0.68	0.45	0	0.21	0.96	0.41	0.15
0.13	0.18	0.86	0.48	0.20	0.44	1.04	0.53	0.14
0.17	0.19	0.72	0.55	0.25	0.41	1.06	0.53	0.13
0.25	0.15	0.69	0.36	0.15	0.51	M	0.37	0.10
0.33	0.17	0.61	0.33	0.06	0.48	0.38	0.34	0.08
0.50	0.12	0.55	0.28	0.04	0.43	0.36	0.30	0.08
0.75	0.10	0.33	0.15	M	0.29	0.39	0.25	0.06
1.00	0.05	0.38	0.16	0.04	0.34	0.41	0.23	0.07
1.50	0.05	0.33	0.13	0	0.31	0.39	0.20	0.07
2.00	0.07	0.29	0.11	0	0.24	0.37	0.18	0.06
3.00	0.04	0.25	0.11	0	0.22	0.31	0.16	0.05
4.00	0.02	0.15	0.07	0	0.20	0.30	0.12	0.05
5.00	M	0.20	0.08	0	0.20	0.29	0.15	0.05
6.00	0.02	0.17	0.09	0	0.22	0.39	0.15	0.06
7.00	M	0.20	0.07	0	0.12	0.29	0.14	0.05
10.00	0	0.12	0.07	0	0.17	0.35	0.12	0.05
13.00	0	0.08	0.07	0	0.17	0.35	0.11	0.05
23.75	0	0.04	0.08	0	0.16	0.57	0.14	0.09
28.00	0	0.10	0.07	0	0.15	0.28	0.10	0.04
36.00	0	0.10	0.06	0	0.13	0.16	0.07	0.03
48.00	0	0.06	0.05	0	0.09	0.29	0.08	0.04
60.00	0	0.06	0.06	0	0.11	0.24	0.08	0.04

* SEM = Standard error of the mean.

Table I continued. Plasma Concentrations of Buprenorphine and Norbuprenorphine after Buprenorphine Administration by the Intravenous, Sublingual, and Buccal Routes of Drug Administration

Time (h)	Subject plasma concentrations (ng/mL) A	C	D	E	G	I	Mean	SEM
1.2-mg norbuprenorphine–intravenous								
72.00	0	0.03	0.03	0	0.12	0.20	0.06	0.03
96.00	0	0	0	0	0.05	0.08	0.02	0.01
4.0-mg buprenorphine–sublingual								
–0.50	0	0	0	0	0	0	0	0
0.04	0.59	0.45	0	0.21	0.75	1.13	0.52	0.16
0.08	1.03	0.65	0.20	0.64	1.19	1.72	0.91	0.22
0.13	1.19	1.15	0.34	0.89	1.35	2.42	1.22	0.28
0.17	1.45	0.12	0.74	0.93	1.72	2.84	1.30	0.38
0.25	1.39	0.85	0.74	1.58	2.35	4.48	1.90	0.57
0.33	2.17	1.49	1.20	1.85	3.26	5.01	2.50	0.58
0.50	2.52	1.12	1.32	2.76	2.95	5.98	2.78	0.71
0.75	M	1.74	2.06	2.09	3.38	7.19	3.29	1.01
1.00	2.06	1.93	2.01	2.50	2.76	5.55	2.80	0.57
1.50	1.33	1.90	1.48	2.03	1.56	3.71	2.00	0.36
2.00	1.38	1.52	1.09	1.58	1.14	3.40	1.69	0.35
3.00	0.86	0.98	0.63	1.00	0.62	2.07	1.03	0.22
4.00	0.37	0.62	0.38	0.41	0.44	1.29	0.59	0.15
5.00	0.49	0.48	0.27	0.64	0.35	1.04	0.55	0.11
6.00	0.35	0.34	0.23	0.41	M	0.73	0.41	0.08
7.00	0.35	0.32	0.19	0.33	0.33	0.88	0.40	0.10
10.00	0.35	0	0.16	0.35	0.34	M	0.24	0.07
13.00	0.33	0.17	0	0.41	M	0.52	0.29	0.09
23.75	0	0	0.17	0.30	0.28	0.43	0.20	0.07
28.00	0	0	0	0.22	0	0.28	0.08	0.05
36.00	0	0	0	0.21	0	0.35	0.09	0.06
48.00	0	0	0	0.19	0	0.17	0.06	0.04
60.00	0	0	0	0	0	0	0	0
72.00	0	0	0	0	0	0	0	0
96.00	0	0	0	0	0	0	0	0
4.0-mg norbuprenorphine–sublingual								
–0.50	0	0	0	0	0	0	0	0
0.04	0.07	0	0	0	0	0	0.01	0.01
0.08	0.09	0	0	0	0	0.04	0.02	0.02
0.13	0.10	0	0.02	0	0	0.06	0.03	0.02
0.17	0.11	0	0.07	0	0	0.06	0.04	0.02
0.25	0.10	0.13	0.10	0.03	0.04	0.10	0.08	0.02
0.33	0.14	M	0.15	0.05	0.12	0.11	0.11	0.02
0.50	0.16	M	0.16	0.15	0.16	0.12	0.15	0.01
0.75	0.14	0.06	0.26	0.17	0.32	0.23	0.20	0.04
1.00	0.24	0.09	0.25	0.40	0.36	0.34	0.28	0.05
1.50	0.22	0.09	0.15	0.38	0.29	0.59	0.29	0.07
2.00	0.22	0.13	0.12	0.41	0.20	M	0.22	0.05
3.00	0.29	0.12	0.08	0.35	0.14	0.59	0.26	0.08
4.00	0.37	0.16	0.05	0.61	0.17	0.47	0.31	0.09
5.00	0.30	0.14	0.05	0.38	0.14	0.64	0.28	0.09
6.00	0.38	0.11	0.04	0.30	M	0.44	0.25	0.08
7.00	0.42	0.09	0.04	0.21	0.12	0.56	0.24	0.08
10.00	0.40	M	0.04	0.22	0.11	0.16	0.19	0.06
13.00	0.36	0.05	0.02	0.23	M	0.33	0.20	0.07
23.75	0.36	0.05	0.06	0.26	0.04	0.48	0.21	0.08

* SEM = Standard error of the mean.
† M = Missing data or measure not taken.

spectrometer was operated in the negative chemical ionization mode. Ammonia was the reagent gas, and argon was the collision gas. Collision-induced dissociation spectra were collected in the selected reaction monitoring mode. Collision chamber conditions were as follows: argon cell pressure, 2.0 millitorr; buprenorphine and buprenorphine-d_4 collision energy, 24 eV; norbuprenorphine collision energy, 20 eV; and norcodeine collision energy, 17 eV.

Research protocol

The research subjects were six men who provided written informed consent and were paid for their participation. The research protocol was approved by the Francis Scott Key Institutional Review Board. The subjects had a history of heroin use but were drug-free at the time of the study. On the basis of physical examination, history, routine laboratory chemistries, and chest x-rays, the participants were in good health and without significant psychiatric disturbances other than drug abuse. The subjects participated while residing on a secured clinical research ward.

An initial intravenous dose-escalation study was performed to ensure that the subjects could tolerate the higher buprenorphine doses given during the protocol. The physiologic and subjective effects on these subjects during the intravenous dose escalation were reported in a previous publication (19).

Buprenorphine was administered in a crossover design study in the following doses and routes of administration: 1.2 mg intravenous, 4.0 mg sublingual, and 4.0 mg buccal. Only one dose was administered to the subjects each week. Intravenous buprenorphine was administered via a catheter in the antecubital vein at a constant rate for 1 min. The sublingual preparation, administered by a Ped-Pod (SoloPak Laboratories, Franklin Park, IL) oral dispenser, consisted of a 30% alcoholic solution that was placed under the tongue for 10 min. The buccal preparation delivery system consisted of a small plastic strip embedded with drug that was placed between the lip and gum for rapid absorption for a period of 10 min. Timed blood samples were collected periodically for 3 days via a catheter in the antecubital vein of the opposite arm from the intravenous

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Time (h)	Subject plasma concentrations (ng/mL) A	C	D	E	G	I	Mean	SEM
4.0-mg norbuprenorphine–sublingual								
28.00	0.35	0.04	0.03	0.20	0.03	0.38	0.17	0.07
36.00	0.34	0	M	0.16	0.03	0.43	0.19	0.08
48.00	0.30	0	0.04	0.14	0	0.48	0.16	0.08
60.00	0.30	0	0.04	0.13	0	0.22	0.12	0.05
72.00	0.17	0	0.03	0.11	0	0.31	0.10	0.05
96.00	0.18	0	0	0.08	0	0.26	0.09	0.05
4.0-mg buprenorphine–buccal								
–0.50	0	0	0	0	0	0	0	0
0.04	0	0	0.20	0	0	0.79	0.17	0.13
0.08	0	0.18	0.20	0	0	1.31	0.28	0.21
0.13	0	0.34	0.40	0.19	0	2.11	0.51	0.33
0.17	0	0.59	0.75	0.21	0	2.81	0.74	0.43
0.25	0.22	1.02	1.96	0.71	0.17	3.30	1.23	0.49
0.33	0.33	1.62	2.37	0.83	0	3.75	1.48	0.57
0.50	0.42	M	2.32	1.24	0.18	3.90	1.61	0.68
0.75	0.62	2.56	2.24	2.15	0.17	3.67	1.90	0.53
1.00	0.63	2.20	2.18	1.94	0.20	2.68	1.64	0.40
1.50	0.48	1.69	1.51	1.43	0.25	2.32	1.28	0.32
2.00	0.38	1.39	1.04	1.13	M	1.64	1.12	0.21
3.00	0.22	0.78	0.57	0.76	M	0.99	0.66	0.13
4.00	0	0.50	0.37	0.59	M	0.71	0.43	0.12
5.00	0	0.34	0.25	0.43	M	0.63	0.33	0.10
6.00	0	0.29	0.17	0.36	0	0.72	0.26	0.11
7.00	0	0.27	0.15	0.31	0	0.55	0.21	0.09
10.00	0	0.24	0.18	0.25	0	0.46	0.19	0.07
13.00	0	0.27	0	0.27	0	0.33	0.15	0.07
23.75	0	0.19	0	0.24	0	0.21	0.11	0.05
28.00	0	0.22	0	0.20	0	0.28	0.12	0.05
36.00	0	0.18	0	0.25	0	0.24	0.11	0.05
48.00	0	0	0	0.17	0	0.24	0.07	0.04
60.00	0	0	0	0.17	0	0	0.03	0.03
72.00	0	0	0	0.16	0	0	0.03	0.03
96.00	0	0	0	0	0	0	0	0
4.0-mg norbuprenorphine–buccal								
-0.50	0	0	0	0	0	0	0	0
0.04	0	0	0	0	0	0.04	0.01	0.01
0.08	0	0	0	0	0	0.18	0.03	0.03
0.13	0	0	0.02	0	0	0.33	0.06	0.05
0.17	0	0	0.03	M	0.02	0.59	0.13	0.12
0.25	0	0	0.11	0.13	0.05	0.81	0.18	0.13
0.33	0	0.02	0.14	0.16	0.03	0.94	0.22	0.15
0.50	0	0.15	0.17	0.28	0.05	0.77	0.24	0.11
0.75	0	0.23	0.20	0.69	0.06	1.26	0.41	0.2
1.00	0	0.23	0.21	0.96	0.09	0.99	0.41	0.18
1.50	0.03	0.24	0.21	0.90	0.17	0.78	0.39	0.15
2.00	0.03	0.37	0.18	0.76	0.10	0.63	0.35	0.12
3.00	0.03	0.24	0.14	0.66	0.08	0.48	0.27	0.1
4.00	0.02	0.20	0.15	0.33	0.08	0.37	0.19	0.06
5.00	0	0.14	0.12	0.34	0.05	0.43	0.18	0.07
6.00	0	0.14	0.11	0.30	0.09	0.31	0.16	0.05

* SEM = Standard error of the mean.
† M = Missing data or measure not taken.

Collection and analysis of blood specimens

Blood samples (5 mL) were collected in heparinized Vacutainer tubes. The samples were centrifuged, and the plasma was transferred to cryotubes and stored frozen until analysis. The plasma samples were analyzed for buprenorphine and norbuprenorphine by negative chemical ionization tandem mass spectrometry according to a previously published procedure (18). Briefly, buprenorphine-d_4 and norcodeine were added as internal standards to 1.5 mL of plasma plus 3 mL 100mM phosphate buffer (pH 6). The samples were mixed and centrifuged. The supernatant was added to a Clean Screen extraction column that was conditioned with 3 mL methanol, 3 mL water, and 1 mL 100mM phosphate buffer (pH 6). The columns were washed with 2 mL water, 2 mL acetate buffer (pH 4.5), and 3 mL methanol. The drugs were eluted from the column with 4 mL methylene chloride–isopropanol–ammonium hydroxide (78:20:2). The eluates were evaporated and derivatized at room temperature with toluene and HFBA. Excess derivatizing reagent was removed by evaporation, and the residue was reconstituted in 20 µL ethyl acetate. An aliquot (4 µL) was injected into the GC for MS–MS analysis. Six-point standard curves and controls were analyzed in duplicate. Between-run percent coefficients of variation for a 0.5-ng/mL plasma control sample were as follows: buprenorphine, 12.8% (N = 52) and norbuprenorphine, 20.4% (N = 46).

Pharmacokinetic analyses

Buprenorphine and norbuprenorphine plasma data were analyzed by nonlinear regression analysis with standard noncompartmental methods. The analysis was performed with PCNONLIN software (Scientific Consulting, Apex, NC). The area under the plasma concentration–time curve (AUC) was calculated by the trapezoidal rule. Extrapolation of the AUC to infinity was determined by dividing the last observed plasma concentration by the terminal elimination rate constant (k_e). The k_e was estimated via linear regression of the points in the linear portion of the time versus log concentration curve. The elimination half-life was derived from $t_{1/2}$ (k_e) = 0.693/k_e. Plasma clearance (CL) after intravenous administration was calculated with the

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