Human Pharmacokinetics of Intravenous, Sublingual, and Buccal Buprenorphine*

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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 sublingual bioavailability was estimated at 55%, although there

* 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., 0.25-μm film thickness). The tandem mass

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) A	C	D	E	G	I	Mean	SEM
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.
† M = Missing data or measure not taken.

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 dose.

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
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 equation

$$CL = \frac{Dose}{AUC(0 -> \infty)} \quad \text{Eq 1}$$

The area under the first moment of the plasma concentration–time curve (*AUMC*) was extrapolated to infinity, and the mean residence time (*MRT*) was derived from *MRT* = *AUMC/AUC*. The intravenous volume of distribution at steady state (V_{ss}) was derived from $V_{ss} = CL \times MRT$. The maximum plasma concentration (C_{max}) and the time to maximum plasma concentration (T_{max}) were obtained by visual inspection of the plasma concentration versus time curves. Bioavailability (*F*) was derived according to the equation

$$F = \frac{AUC(\text{route})}{AUC(\text{intravenous})} \times \frac{Dose(\text{intravenous})}{Dose(\text{route})} \quad \text{Eq 2}$$

The average initial volume of distribution divided by the fraction of an absorbed sublingual and buccal dose was calculated from $Vd/F = Dose/(AUC \times k_e)$. The average total clearance divided by the fraction of an absorbed sublingual and buccal dose was calculated from $CL/F = Dose/AUC$.

Statistics

Differences among the three routes of administration were analyzed for statistical significance using a repeated measures single-factor analysis of variance (ANOVA). The ANOVA was used to test the null hypothesis of no significant difference at an alpha level of 0.05. A Newman-Keuls test was used to determine significant differences among pharmacokinetic parameters at $p < .05$.

Results

Plasma concentrations of buprenorphine and norbuprenorphine from six male subjects were measured by negative chemical ionization tandem mass spectrometry. The technique was developed to measure both parent drug and metabolite simultaneously in biological fluids at subnanogram-per-milliliter concentrations. The limit of detection (LOD) for buprenorphine was 0.15 ng/mL, and the limit of quantitation (LOQ) was 0.20 ng/mL. The LOD for norbuprenorphine was 0.016 ng/mL, and the LOQ was 0.031 ng/mL.

Individual subject and mean plasma concentrations of buprenorphine and norbuprenorphine for intravenous, sublingual, and buccal routes of administration are presented in Table I. Plasma concentrations less than the LOQ but greater than the LOD were included in Table I. The inclusion of these plasma concentrations allowed better estimates of pharmacokinetic parameters. Six subjects completed the entire study. Subject ages and weights are presented in Table II. Intravenous buprenorphine data from subject D were lost because of an analytical error, but norbuprenorphine measurements were unaffected. After a 1.2-mg intravenous buprenorphine dose, peak plasma concentrations ranged from 24.40 to 55.98 ng/mL (mean peak, 37.52 ng/mL; $N = 5$). Individual subject plasma concentrations declined below the assay's LOD between 13 and 48 h. After 4.0-mg buprenorphine doses by the sublingual and buccal routes of administration, peak sublingual buprenorphine plasma concentrations occurred at an average time of 0.71 h (range, 0.50–1.00 h; $N = 6$), and buccal buprenorphine plasma concentrations peaked at an average time of 0.81 h (range, 0.33–1.50 h; $N = 6$). The average maximum buprenorphine plasma concentration after sublingual administration was 3.31 ng/mL (range, 1.93–7.19 ng/mL), whereas the average maximum buprenorphine plasma concentration after buccal administration was 1.98 ng/mL (range, 0.25–3.90 ng/mL). Both sublingual and buccal buprenorphine plasma concentrations were detected for a longer period of time than the intravenous buprenorphine plasma concentrations. The subjects' sublingual buprenorphine plasma concentrations declined below the LOD from 23.75 to 60 h after dose administration, and the buccal plasma buprenorphine concentrations fell below the LOD from 4 to 96 h.

Statistical analysis by ANOVA indicated that the buprenorphine peak times and

Table II. Subject Ages and Weights

Subject	Age (yrs)	Weight (lbs/kg)
A	40	154/69.8
C	34	147/66.7
D*		
E	36	138/62.6
G	27	160/72.7
I	35	147/66.5

* Information was unavailable.

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
4.0-mg norbuprenorphine–buccal								
7.00	0	0.16	0.10	0.27	0.06	0.33	0.15	0.05
10.00	0	0.10	0.10	0.23	0.06	0.22	0.12	0.04
13.00	0	0.25	0.20	0.26	0.05	0.21	0.16	0.04
23.75	0	0.21	0.11	0.27	0.03	0.18	0.13	0.04
28.00	0	0.13	0.10	0.28	0.05	0.21	0.13	0.04
36.00	0	0.12	0.09	0.29	0.07	0.42	0.17	0.06
48.00	0	0.07	0.09	0.19	0.08	0.16	0.10	0.03
60.00	0	0.04	0.09	0.22	0.05	0.17	0.10	0.03
72.00	0	0	0.11	0.16	0.04	0.09	0.07	0.03
96.00	0	0	0.05	0.14	0	0.02	0.04	0.02

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

peak concentrations were significantly different among the three routes of administration. Intravenous peak times were significantly less ($p < .01$) and peak concentrations were significantly greater ($p < .01$) than sublingual and buccal routes of administration.

The *N*-dealkyl metabolite, norbuprenorphine, appeared in the plasma immediately after intravenous administration in low concentrations and reached an average peak plasma concentration at 0.18 h. Peak plasma concentrations after intravenous administration ranged from 0.19 to 1.06 ng/mL (mean, 0.57 ng/mL; $N = 6$). Norbuprenorphine appeared initially in plasma after sublingual administration in one subject at 0.04 h and in all other subjects at 0.25 h. The average peak concentration was 0.41 ng/mL (range, 0.16–0.64 ng/mL; $N = 6$), and the average peak time was 3.63 h. After buccal administration, norbuprenorphine appeared in one subject at 0.04 h and in all other subjects at 0.33 h, except for subject A. Norbuprenorphine concentrations peaked after buccal administration at 1.29 h (range, 0.7–2.00 h; $N = 6$) at an average concentration of 0.50 ng/mL (range, 0.03–1.26 ng/mL; $N = 6$). All three routes of administration had similar peak norbuprenorphine plasma concentrations, but the peak concentrations occurred at different times. Norbuprenorphine continued to be detected in some subjects' plasma for 96 h.

Norbuprenorphine peak concentrations were not significantly different among the three routes of administration, but the time to peak concentration was significantly different. Peak times for norbuprenorphine by the intravenous route were found to be significantly less ($p < .01$) than by the sublingual route, and the buccal route times were significantly less ($p < .05$) than by the sublingual route.

Pharmacokinetic parameters for each subject after intravenous, sublingual, and buccal routes of administration are presented in Tables III–V. Buprenorphine AUCs by the intravenous, sublingual, and buccal routes of administration were not significantly different ($p < .05$). The elimination half-life by the intravenous route (mean, 3.21 h; range, 1.62–8.18 h) was significantly less ($p < .05$) than the sublingual elimination half-life, but it was not significantly different than the buccal elimination half-life ($p < .05$). Comparison of half-lives of buprenorphine by the sublingual (mean, 27.72 h; range, 5.21–49.09 h) and buccal (mean, 19.01 h; range, 1.32–48.63 h) routes indicated that they were not significantly different ($p < .05$). The average bioavailability for the sublingual route of administration (mean, 51.4%; range, 12.8–92.2%; $N = 5$) was not significantly different ($p < .05$) than that observed for the buccal route of administration (mean, 27.8%; range, 4.1–42.7%; $N = 4$).

Estimated elimination half-lives for norbuprenorphine were longer than for buprenorphine. The mean half-lives for norbuprenorphine were as follows: 35.56 h (range, 1.11–66.78 h) by the intravenous route; 83.0 h (range, 9.7–216.3 h) by the

Table III. Pharmacokinetic Parameters* of Buprenorphine and Norbuprenorphine after a Single Intravenous Dose (1.2 mg) of Buprenorphine

	Parameters										
Subjects	T_{max} (h)	C_{max} (ng/mL)	k_e (1/h)	$t_{1/2}(k_e)$ (h)	AUC (h•ng/mL)	AUMC (h^2•ng/mL)	MRT (h)	CL (L/h)	V_{ss} (L)	No. Obs.	AUC(N)/AUC(B)
Buprenorphine											
A	0.04	37.83	0.39	1.77	11.81	29.24	2.48	101.6	251.5	17	–
C	0.04	43.93	0.43	1.62	21.58	48.39	2.24	55.6	124.6	17	–
D	M†	M	M	M	M	M	M	M	M	M	–
E	0.04	25.60	0.08	8.18	21.36	293.1	13.72	56.2	770.8	21	–
G	0.04	24.40	0.32	2.17	10.41	32.52	3.12	115.3	360.2	17	–
I	0.04	55.83	0.30	2.31	21.72	65.81	3.03	55.2	167.3	17	–
Mean	0.04	37.52	0.30	3.21	17.38	93.8	4.92	76.8	334.9	–	–
SEM‡	0	5.88	0.06	1.25	2.57	50.24	2.21	13.1	116.2	–	–
Norbuprenorphine											
A	0.17	0.19	0.26	2.71	0.36	–	–	–	–	15	0.03
C	0.13	0.86	0.03	26.36	7.53	–	–	–	–	24	0.35
D	0.17	0.55	0.01	62.25	7.76	–	–	–	–	24	M
E	0.17	0.25	0.62	1.11	0.12	–	–	–	–	6	0.01
G	0.25	0.51	0.01	66..78	16.94	–	–	–	–	25	1.63
I	0.17	1.06	0.01	54.13	29.13	–	–	–	–	23	1.34
Mean	0.18	0.57	0.16	35.56	10.31	–	–	–	–	–	0.67
SEM	0.02	0.14	0.10	12.09	4.53	–	–	–	–	–	0.34

* T_{max} = Time to maximum plasma concentration, C_{max} = Maximum plasma concentration, k_e = Elimination rate constant, $t_{1/2}(k_e)$ = Elimination half-life, AUC = Area under the plasma concentration–time curve, AUMC = Area under the first moment curve, MRT = Mean residence time, CL = Clearance, V_{ss} = Volume of distribution at steady state, No. Obs. = Number of observations, AUC(N)/AUC(B) = Ratio of the norbuprenorphine area under the plasma concentration–time curve to the buprenorphine area under the plasma concentration–time curve.

† M = Parameter could not be determined.

‡ SEM = Standard error of the mean.

sublingual route; and 73.63 h (range, 13.42–143.06 h) by the buccal route. Statistical analysis indicated that there were no significant differences ($p < .05$) among the three routes of administration for the terminal elimination half-lives, areas under the curve, and ratio of area under the curve of metabolite to parent drug. The time to peak plasma norbuprenorphine concentration by sublingual administration was significantly longer than by the intravenous ($p < .01$) and buccal ($p < .05$) routes of administration.

Discussion

Buprenorphine is a partial agonist with a long duration of action. It is well-tolerated at the higher doses required for the treatment of opioid addiction, and cessation of drug administration produces mild withdrawal symptoms. The effectiveness of buprenorphine by the sublingual route has a decided advantage over other medications that require parental administration. Sublingual plasma buprenorphine concentrations were shown to increase linearly as a function of dose (2,6); however, most pharmacokinetic studies have evaluated only analgesic dosages. Bullingham et al. (6) evaluated sublingual buprenorphine pharmacokinetics at doses of 0.4 and 0.8 mg in 15 postoperative patients. Buprenorphine reached peak plasma concentrations at approximately 3.35 h (range, 1.5–6 h), and the absolute systemic availability was estimated at 55% (range, 15.5–94.4%). The elimination half-life of buprenorphine was estimated to be approximately 3–5 h for both the intravenous and the sublingual routes of administration. In the present study, sublingual dosages 5–10 times greater than those used by Bullingham et al. (6) were administered to reflect dosages in the range given in clinical treatment studies (7–10,20–24). The 1.2-mg intravenous and 4.0-mg sublingual and buccal doses of buprenorphine were estimated to be bioequivalent among the three routes of administration. Comparison of linear elimination phases of the sublingual and buccal curves in Figure 1A indicated that sublingual administration produced higher concentrations than did the buccal route. Sublingual bioavailability was estimated at 51.4% (range, 12.8–92.2%), which is in excellent agreement with the previous work by Bullingham et al. (6). Buccal bioavailability, although not significantly different, was less than sublingual bioavailability (27.8%; range, 4.1–42.7%).

The mean time to peak plasma buprenorphine concentrations by the sublingual route of administration was 0.71 h (range, 0.50–1.00 h). This time was approximately one-fifth the time reported by Bullingham et al. (6) (mean, 3.35 h; range, 1.5–6 h) but was in agreement with Walsh et al. (2), who reported an estimated peak plasma concentration time of 1.0 h after administration of 2- and 4-mg doses and a time of 0.5 h

Table IV. Pharmacokinetic Parameters* of Buprenorphine and Norbuprenorphine after a Single Sublingual Dose (4.0 mg) of Buprenorphine

	Parameters											
Subjects	T_{max} (h)	C_{max} (ng/mL)	k_e (1/h)	$t_{1/2}(k_e)$ (h)	AUC (h•ng/mL)	AUMC (h^2•ng/mL)	MRT (h)	F (%)	CL/F (L/h)	Vd/F (L)	No. Obs.	AUC(N)/AUC(B)
Buprenorphine												
A	0.50	2.52	0.020	35.34	25.31	1112	43.9	64.3	158.1	8060	17	–
C	1.00	1.93	0.133	5.21	9.24	56	6.0	12.8	433.0	3256	17	–
D	0.75	2.06	0.028	25.03	13.92	422	30.3	M†	287.3	10,376	18	–
E	0.50	2.76	0.022	31.91	27.30	1112	40.7	38.3	146.5	6746	22	–
G	0.75	3.38	0.014	49.09	31.99	1966	61.5	92.2	125.0	8857	17	–
I	0.75	7.20	0.035	17.74	35.57	797	22.1	49.1	112.5	3203	21	–
Mean	0.71	3.31	0.042	27.72	23.89	910	34.1	51.4	210.4	6750	–	–
SEM‡	0.08	0.81	0.02	6.08	4.20	269	7.83	13.2	51.4	1212	–	–
Norbuprenorphine												
A	7.00	0.42	0.01	62.7	43.3	–	–	–	–	–	25	1.71
C	4.00	0.16	0.07	9.7	6.4	–	–	–	–	–	12	0.69
D	0.75	0.26	0.005	143.6	9.3	–	–	–	–	–	18	0.67
E	4.00	0.61	0.01	53.8	22.2	–	–	–	–	–	21	0.81
G	1.00	0.36	0.06	12.2	3.5	–	–	–	–	–	15	0.11
I	5.00	0.64	0.003	216.3	115.4	–	–	–	–	–	23	3.25
Mean	3.63	0.41	0.03	83.0	33.35	–	–	–	–	–	–	1.21
SEM	0.98	0.08	0.01	33.2	17.47	–	–	–	–	–	–	0.46

* T_{max} = Time to maximum plasma concentration, C_{max} = Maximum plasma concentration, k_e = Elimination rate constant, $t_{1/2}(k_e)$ = Elimination half-life, AUC = Area under the plasma concentration–time curve, AUMC = Area under the first moment curve, MRT = Mean residence time, F = Bioavailability, CL/F = Clearance/availability, Vd/F = Apparent volume of distribution/availability, No. Obs. = Number of observations, AUC(N)/AUC(B) = Ratio of the norbuprenorphine area under the plasma concentration–time curve to the buprenorphine area under the plasma concentration–time curve.

† M = Parameter could not be determined.

‡ SEM = Standard error of the mean.

after administration of 8-, 16-, and 32-mg doses. These differences may be due in part to the sublingual formulations used. In the present study, a 30% alcoholic solution was placed under the tongue and held for 10 min. In the study by Walsh et al. (2), a 40% alcoholic solution was administered. Bullingham et al. (6) administered buprenorphine in tablet form by the sublingual route. Tablet dissolution could have been a factor in the delayed times to peak concentrations.

The pharmacokinetic profile of buprenorphine by intravenous administration has been studied more thoroughly than the profile of buprenorphine by sublingual administration. Bullingham et al. (12) measured plasma concentrations in 10 patients who received 0.3 mg of buprenorphine intravenously for postoperative pain relief. The average estimated plasma clearance for those 10 patients was 76.5 L/h. Olkkola et al. (14) reported a mean buprenorphine plasma clearance in children of 77.0 L/h after an intravenous 0.3-mg/kg dose. The mean plasma clearance in this study after a 1.2-mg buprenorphine intravenous dose was 76.8 L/h (range, 55.6–115.3 L/h; $N = 5$). The apparent volume of distribution at steady state (mean, 334.9 L; range, 124.6–770.8 L) also agrees with studies by Bullingham et al. (12) (*Vd* was equal to 187.8 L), Olkkola et al. (14) (*Vd* was equal to 166.6 L), and Bullingham et al. (25) (*Vd* was equal to 200–400 L). These high V_{ss} estimates are often associated with highly lipophilic drugs, such as buprenorphine, that undergo rapid distribution to tissues, which results in low plasma concentrations.

The terminal half-life of buprenorphine appears to vary with the length of time plasma was collected and with the sensitivity of the analytical technique. For example, a 3-h plasma terminal elimination half-life was reported by Bullingham et al. (12), but sampling occurred only for 3 h. When the plasma collection time was increased to 13 h, the estimate of the terminal elimination half-life increased to 5 h (6). Ho et al. (13) reported a plasma terminal elimination half-life of 3.83 h in one patient, and plasma samples were collected for a 3.67-h period using high-performance liquid chromatography with fluorescence detection and a sensitivity of 1 ng/mL. In the present study, the buprenorphine mean terminal elimination half-lives varied among routes of administration. After a 1.2-mg intravenous buprenorphine dose, the elimination half-life was estimated at 3.21 h (range, 1.62–8.18 h; $N = 5$). After 4.0-mg doses, the sublingual elimination half-life was estimated as 27.72 h (range, 5.21–49.09 h), and the buccal elimination half-life was estimated as 19.01 h (range, 1.32–48.63 h).

The intravenous elimination half-life found in this study is in agreement with the studies of Bullingham et al. (12) and Ho et al. (13); however, the sublingual and buccal terminal elimination half-lives are considerably longer. Figure 1A demonstrates that the elimination phase of buprenorphine appears to be similar by all three routes of administration. At approximately 13 h, the sublingual and buccal plots plateau, whereas the intravenous plot continues its linear decay. Sublingual and buccal plots remain above the LOD for approximately

Table V. Pharmacokinetic Parameters* of Buprenorphine and Norbuprenorphine after a Single Buccal Dose (4.0 mg) of Buprenorphine

	Parameters											
Subjects	T_{max} (h)	C_{max} (ng/mL)	k_e (1/h)	$t_{1/2}(k_e)$ (h)	AUC (h•ng/mL)	AUMC (h^2•ng/mL)	MRT (h)	F (%)	CL/F (L/h)	Vd/F (L)	No. Obs.	AUC(N)/AUC(B)
Buprenorphine												
A	1.00	0.63	0.53	1.32	1.61	3.7	2.32	4.1	2484	4732	8	–
C	0.75	2.56	0.04	17.99	17.31	434.8	25.12	24.1	231.1	5998	19	–
D	0.33	2.37	0.16	4.20	6.96	32.1	4.62	M†	575.0	3489	17	–
E	0.75	2.15	0.01	48.63	30.43	2101	69.04	42.7	131.4	9224	22	–
G	1.50	0.25	M	M	M	M	M	M	M	M	5	–
I	0.50	3.90	0.03	22.92	29.08	954.9	32.83	40.2	137.5	4548	22	–
Mean	0.81	1.98	0.15	19.01	17.08	705.4	26.79	27.8	711.9	5598	–	–
SEM‡	0.17	0.55	0.10	8.44	5.76	389.2	12.07	8.9	450.5	990	–	–
Norbuprenorphine												
A	1.50	0.03	M	M	M	–	–	–	–	–	4	M
C	2.00	0.37	0.05	13.42	9.46	–	–	–	–	–	19	0.55
D	1.00	0.21	0.01	90.87	16.46	–	–	–	–	–	23	2.37
E	1.00	0.96	0.01	93.28	41.26	–	–	–	–	–	21	1.36
G	1.50	0.17	0.005	143.1	12.46	–	–	–	–	–	21	M
I	0.75	1.26	0.03	27.51	19.76	–	–	–	–	–	25	0.68
Mean	1.29	0.50	0.02	73.63	19.88	–	–	–	–	–	–	1.24
SEM	0.19	0.20	0.01	23.72	5.62	–	–	–	–	–	–	0.42

* T_{max} = Time to maximum plasma concentration, C_{max} = Maximum plasma concentration, k_e = Elimination rate constant, $t_{1/2}(k_e)$ = Elimination half-life, AUC = Area under the plasma concentration–time curve, AUMC = Area under the first moment curve, MRT = Mean residence time, F = Bioavailability, CL/F = Clearance/availability, Vd/F = Apparent volume of distribution/availability, No. Obs. = Number of observations, AUC(N)/AUC(B) = Ratio of the norbuprenorphine area under the plasma concentration–time curve to the buprenorphine area under the plasma concentration–time curve.

† M = Parameter could not be determined.

‡ SEM = Standard error of the mean.

13–28 h, which results in the calculation of a longer terminal elimination half-life. The terminal elimination beyond approximately 13 h may not represent a true terminal elimination but a slow elimination produced by the release of buprenorphine from sequestered sites possibly in the oral mucosa. Release of buprenorphine from sequestered sites into the plasma would be rate-limiting, and its rate of absorption into the plasma would be slower than the elimination rate ("flip flop" model). The finding that the intravenous route's terminal elimination does not plateau in the same manner as the buccal and sublingual routes' terminal elimination suggested this depot effect. A proposed model is represented in Figure 2. Some evidence that may support a depot effect from buprenorphine in the oral mucosa was reported by Cone et al. (26). Saliva levels after acute intramuscular administration were substantially less than plasma levels. In contrast, concentrations of buprenorphine in saliva remained highly elevated during the first 12 h after sublingual administration. The continued presence of buprenorphine in saliva after sublingual administration suggests that a "shallow depot" was produced after sublingual administration.

No pharmacokinetic information appears to have been published on norbuprenorphine in humans. Plasma concentrations of norbuprenorphine were 4–66 times lower than buprenorphine when comparing the ratio of peak plasma concentrations of buprenorphine with norbuprenorphine across the three routes of administration. Mean norbuprenorphine peak concentrations occurred between 0.18 and 3.63 h, and the terminal elimination half-lives of norbuprenorphine were longer than buprenorphine (Figure 1B).

In the present study, buprenorphine and norbuprenorphine concentrations were highly variable within and among the different routes of administration. There was much greater variability in norbuprenorphine pharmacokinetic parameters among subjects than for buprenorphine. As evident from the between-run coefficients of variation, part of the variability can be ascribed to the new analytical method used for measurement of buprenorphine and norbuprenorphine at very low concentrations. A large portion of the variability was undoubtedly because of individual subject variability and the limited number of subjects in the study. Unfortunately, insufficient sample volume precluded repeat analyses. Although the variability in this study was greater than desired, many of the buprenorphine pharmacokinetic parameters were consistent with previously reported data (2,6,12–14,25).

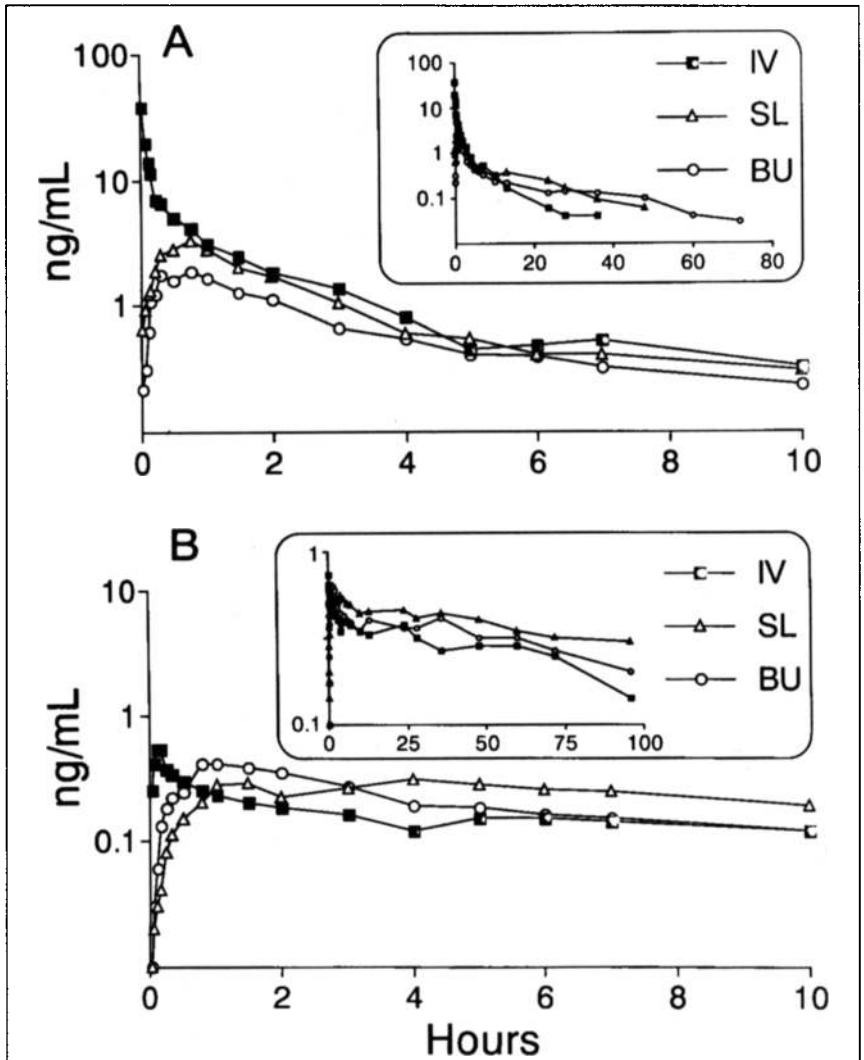

Figure 1. Mean plasma concentrations of (A) buprenorphine and norbuprenorphine (B) during the first 10 h after administration of single doses of buprenorphine by the intravenous (IV) (1.2 mg), sublingual (SL) (4.0 mg), and buccal (BU) (4.0 mg) routes to six human subjects. One subject (subject D) was not included in the data for intravenous route of administration. The insets illustrate the buprenorphine and norbuprenorphine plasma concentrations for the entire period plasma samples were measured.

In summary, this study presents a detailed pharmacokinetic analysis of buprenorphine in plasma for an extended collection period after administration to human subjects by three different routes. In addition, the pharmacokinetics of the active metabolite, norbuprenorphine, were evaluated for the first time. Much of the previous buprenorphine pharmacokinetic information obtained by radioimmunoassay agreed with the current pharmacokinetic estimates obtained by mass spectrometry. The systemic availability of buprenorphine by the sublingual route of administration was greater than the buccal bioavailability. The extended elimination half-lives of the sublingual and buccal administration routes may have been due to a depot effect that could be advantageous in the treatment of opioid dependence.

Acknowledgments

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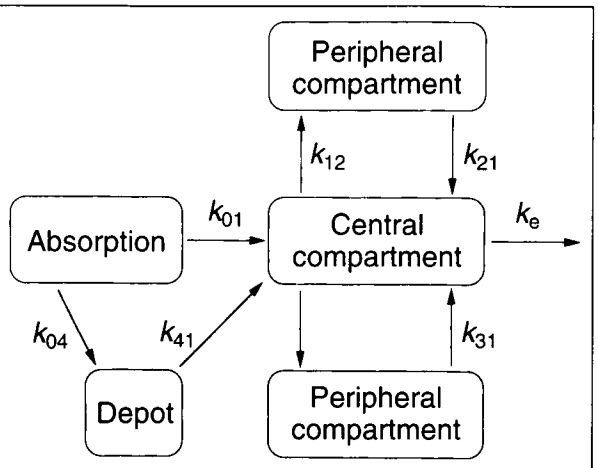

Figure 2. Proposed model of the sublingual and buccal depot effect after administration of 4.0 mg of buprenorphine. Rate $k_{41} << k_e$.

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