

# Pharmacokinetic and Pharmacodynamic Properties of Buprenorphine After a Single Intravenous Administration in Healthy Volunteers: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study

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## ABSTRACT

**Background:** Buprenorphine is used as an analgesic for postoperative and chronic pain. The usual sublingual dose is 0.2 to 0.8 mg, and the usual parenteral dose is 0.3 mg for acute postoperative pain. The pharmacokinetic and related pharmacodynamic properties of buprenorphine at these doses have not been characterized.

**Objective:** The aim of this study was to assess the pharmacokinetic properties of buprenorphine 0.002 mg/kg IV (0.15 mg/70 kg) and its antinociceptive and psychomotor effects.

**Methods:** Healthy male volunteers received 0.002 mg/kg buprenorphine IV in a randomized, double-blind, placebo-controlled, crossover design. Blood samples were collected at 0.5, 1, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, and 8 hours for the determination of plasma concentrations. Pharmacokinetic parameters were estimated by a compartmental model using specialized software. Antinociceptive and psychomotor effects were determined for 8 hours. Quantitative sensory testing with thermal and electrical (nociceptive flexion RIII reflex) stimulations was performed. The cold pressor test was used to assess pain tolerance to a tonic, intense pain stimulation. Psychomotor performance was assessed by the digit symbol substitution test (DSST). Participants also rated sedation on an 11-point numeric scale (0 = none to 10 = severe). A selective liquid chromatography–tandem mass spectrometry assay was developed for the determination of buprenorphine; the limit of quantification was 0.05 ng/mL using a 0.25-mL plasma aliquot. Participants were instructed to report adverse effects, which were recorded for type, time of onset, seriousness, and duration.

**Results:** The study enrolled 12 participants, all of whom were white. Mean (SD) age was 26 (3.5) years, and mean weight was 67 (9) kg. None of the participants had a history of opiate abuse. Buprenorphine significantly increased the objective (nociceptive flexion RIII reflex) and subjective pain thresholds for >4 hours and pain tolerance (cold pressor test) for 2 hours. The mean (SD) RIII reflex threshold and subjective threshold at baseline were 31.6 (9.5) mÅ and 45.5 (22.3) mÅ, respectively. The maximum increases (mean [SD]) were +14.1 (17.5) mÅ for the RIII reflex ( $P = 0.02$ ) and +24.2 (21.7) mÅ for the subjective threshold ( $P = 0.02$ ), corresponding to mean (SEM) percentages of 53.7% (20.2%) and 74.7% (20.4%) of the baseline values, respectively. The maximum increases were observed at 120 minutes for both measures. The effect of buprenorphine on pain tolerance peaked at 30 minutes. Mean (SEM) latency before withdrawal of the hand was 69 (10) seconds, corresponding to a mean increase of 63.8% (14.4%) from baseline ( $P = 0.003$ ). Buprenorphine had a significant effect on the DSST. The mean maximum decrease in the total number of symbols drawn was -6 (14.5%;  $P = 0.005$ ) at 1 hour. The participants reported high levels of sedation: at peak effect (120 minutes), mean scores increased from 2.9 to 6.4 (SEM 0.7) ( $P = 0.005$ ). Levels returned to baseline values by the end of the session, unlike for the nociceptive tests. The onset of effects

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occurred during the distribution phase for all the measures, and their duration was observed across a wide range of concentrations during the elimination phase. The most likely explanation for this finding is the high affinity of buprenorphine at  $\mu$ -opioid receptors, and possibly distribution to the brain. Buprenorphine  $t_{1/2}$  was 2.75 hours. A secondary peak in concentration was observed at 90 minutes, suggesting enterohepatic circulation of buprenorphine. A 2-compartment model adequately described buprenorphine pharmacokinetics.

**Conclusions:** A clinically relevant analgesic dose of 0.002 mg/kg (0.15 mg/70 kg) of buprenorphine had a significant effect on nociception and psychomotor performance in these healthy male volunteers. A 2-compartment model satisfactorily characterized buprenorphine pharmacokinetics, and we found evidence of enterohepatic circulation. (*Clin Ther.* 2007;29:1620–1631) Copyright © 2007 Excerpta Medica, Inc.

**Key words:** buprenorphine, pharmacokinetics, pain, pharmacodynamics.

## INTRODUCTION

Buprenorphine is a semisynthetic oripavine derivative that acts as a partial agonist at  $\mu$ -opioid receptors. It is used as an analgesic, and the usual sublingual dose is 0.2 to 0.8 mg every 6 to 8 hours.<sup>1</sup> The usual parenteral dose to relieve acute postoperative pain is 0.3 mg.<sup>2,3</sup> Bioavailability by the sublingual route is between 30% and 50%.<sup>4,5</sup> Buprenorphine has a high affinity for ( $K_i = 0.31$  nM)<sup>6</sup> and a slow dissociation constant from ( $K_{D \text{ in vitro}} = 1$  nM)<sup>7</sup> the opioid receptor, which can explain its long duration of action (6–8 hours).<sup>8,9</sup> Dissociation is characterized by an initial rapid phase ( $t_{1/2}$ ,  $k_{off} = 5.6$  minutes) followed by a slower phase ( $t_{1/2}$ ,  $k_{off} = 166.4$  minutes).<sup>7</sup> It is *N*-dealkylated into norbuprenorphine by hepatic cytochrome P450 3A4, with further glucuronidation of both buprenorphine and its metabolite.<sup>10,11</sup> Experimental evidence suggests that the *N*-dealkylated metabolite does not contribute to the antinociceptive effect of buprenorphine.<sup>12</sup>

Current analytic methods are not sensitive enough for the determination of blood buprenorphine concentrations at low doses such as those used to treat pain. Therefore, its pharmacokinetics and related pharmacodynamics at clinically relevant analgesic doses have not been characterized, based on a search of the literature (MEDLINE; key terms: *buprenorphine*, *pharmacoki-*

*netics*, *pharmacology*, *biopharmaceuticals*, *drug effects*, *physiological effects of drugs*, *pain*, *pain measurement*, *nociceptive tests*, *pain threshold*, *analgesia*, and *neuropsychological tests*. We developed a selective liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay for the determination of buprenorphine. We assessed the pharmacokinetics of an IV dose of 0.002 mg/kg (0.15 mg/70 kg) and its antinociceptive and psychomotor effects. The data were collected as part of a study on the efficacy of naltrexone, a pure synthetic opioid antagonist, in reversing the action of buprenorphine. That part of the experiment will be the subject of another paper. The chosen dose of buprenorphine was in the range of those used to treat pain in clinical settings.

## SUBJECTS AND METHODS

### Participants

Healthy male adult volunteers were eligible for the study. None of the participants had a history of opiate abuse. They had unremarkable medical history and physical examination, were nonsmokers, and reported not taking any drugs for a month before the study. The participants gave written informed consent and were compensated for their participation. The study protocol and consent form were approved by the Ethics Committee of the Geneva University Hospitals. The study was conducted according to the principles in the Declaration of Helsinki.<sup>13</sup>

### Study Drug Administration

The marketed injectable solution of buprenorphine hydrochloride\* was supplied by the pharmacy of the Geneva University Hospitals. The pharmacy prepared the naltrexone and placebo capsules according to standard procedures and the blinding requirements. Naltrexone was prepared in a gelatin capsule. One 50-mg tablet (Bristol-Myers Squibb GmbH, Baar, Switzerland) was crushed and mixed with sufficient mannitol to fill the capsule. Naltrexone is rapidly and completely absorbed from the gastrointestinal tract, and there is no reason that crushing the tablet should alter its bioavailability. Moreover, our preliminary analysis of naltrexone pharmacokinetics showed that its  $C_{max}$  and  $T_{max}$  when given with IV placebo corresponded to published data. Placebo ampules contained normal saline and placebo capsules contained mannitol.

\*Trademark: Temgesic® (Essex Chemie AG, Luzern, Switzerland).

### Study Design

The study was randomized, double blind, placebo controlled, and crossover. Randomization was done by blocks of 5, using the Latin square method. The primary end point of the study was an increase in the objective pain threshold as determined by the nociceptive flexion RIII reflex. Sample size (12 subjects) was calculated so that a 30% increase in nociception could be detected with 70% power. The participants were administered a weight-adjusted dose of 0.002 mg/kg of buprenorphine. Hence, a volunteer weighing 70 kg would receive 0.15 mg buprenorphine.

Each participant received 1 of the following: (1) a single IV injection of 0.002 mg/kg buprenorphine followed 45 minutes later by 50 mg naltrexone PO, (2) placebo followed by naltrexone, or (3) buprenorphine followed by placebo. Washout periods lasted at least 2 weeks between the sessions. After an overnight fast, the participants were admitted to the clinical research unit early in the morning of the study day. Buprenorphine was administered in a 1-mL volume over 1 minute through a catheter inserted into an antecubital vein. Participants were recumbent throughout the experiment and were served a standard meal 4 hours after dosing. They were given orange juice every hour to prevent variations in blood glucose and pain threshold.<sup>14</sup> Blood (8 mL per sample) was collected in EDTA tubes from the indwelling catheter at 0.5, 1, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, and 8 hours after the administration of buprenorphine. Samples were centrifuged at 3000 rpm for 10 minutes. Plasma was collected, split into 2 aliquots, and stored at  $-30^{\circ}\text{C}$  until assayed.

Pharmacodynamic tests were performed before drug dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours afterward. The sequence of the tests was the same throughout the session. At the start of each assessment, the participants were asked to rate sedation; then they performed the digital symbol substitution test (DSST). This was followed by the quantitative sensory testing because the various tasks require good attention from the participant. The cold pressor test was the last measure done because it can activate diffuse noxious inhibitory controls and inhibit the nociceptive flexion RIII reflex.<sup>15,16</sup>

### Buprenorphine Assay

A selective LC-MS/MS assay was developed at the Geneva University School of Pharmaceutical Sciences for the determination of buprenorphine in human

plasma. The validation procedure was based on guidelines of the US Food and Drug Administration and the International Conference on Harmonisation for bioanalytic method validation of human studies. The assay used liquid chromatography combined with electrospray ionization tandem mass spectrometry detection on a triple quadrupole linear ion trap mass spectrometer. For sample preparation, the method involved liquid-liquid extraction. The analytes were separated on a reversed-phase column in gradient mode and detected in the positive selected reaction monitoring mode. The validated method was accurate and precise across the dynamic range of 0.05 to 50 ng/mL using a 0.25-mL plasma aliquot. The mean precision and accuracy, calculated from the quality controls (QCs), were 8.2% and 106%, respectively. The data were assessed from QC samples during analysis of study samples.

### Analytic Method Description

Into a 1.5-mL Eppendorf tube, we added 25  $\mu\text{L}$  of internal standards (buprenorphine-D4 and naloxone) in water/methanol (1:1) and 10  $\mu\text{L}$  of triethylamine 10% aqueous to 250  $\mu\text{L}$  of plasma, then added 1 mL of n-BuCl/MeCN (4:1 v/v). After extraction, the organic phase was transferred to clean tubes, evaporated to dryness after centrifugation ( $\sim 14,000g$ , 10 minutes at  $20^{\circ}\text{C}$ ), and reconstituted with 100  $\mu\text{L}$  of 1% formic acid in water/methanol (90:10 v/v). Aliquots of 30  $\mu\text{L}$  were injected using an auto sampler (model SIL HTC, Shimadzu, Columbia, Maryland) onto an analytic chromatographic column X-Terra C18 (5  $\mu\text{m}$ , 2.1  $\times$  150 mm; Waters, Milford, Massachusetts). The flow rate was 0.3 mL/min. Solvent A consisted of a mixture of 1% formic acid in water, whereas solvent B was 1% formic acid in methanol. The gradient started after 0.5 minute from 10% B. The organic content was then increased to 50% B within 0.5 minute, held for 0.5 minute, increased again to 90% B within 2 minutes, and maintained for 1 minute.

A triple quadrupole linear ion trap mass spectrometer (4000-QTRAP; AB/MDS Sciex, Concord, Ontario, Canada) equipped with an electrospray source was used to detect the analytes. The whole effluent (0.3 mL/min) of the analytic column was introduced into the turbo V source operated at a temperature of  $450^{\circ}\text{C}$ . Nitrogen was used as nebulizer, curtain, and collision gas. For the single reaction monitoring (SRM) quantita-

tion, the following transitions were used: buprenorphine,  $m/z$  468.4– $m/z$  55.0, and buprenorphine-D4 (IS),  $m/z$  472.4– $m/z$  59.0. The dwell times were set at 75 ms for the analyte and for the internal standard. The collision energy for fragmentation of the precursor ions was set at 94 eV and 93 eV for buprenorphine and buprenorphine-D4, respectively. The declustering potential was set at 111 eV and 121 eV for buprenorphine and buprenorphine-D4, respectively. The mass calibration of both the separating quadrupoles Q1 and Q3 was set to 0.7 Da FWHM (full width at half maximum) for both precursor and product ions.

#### **Calibration Curves, Quality Controls, and Sample Analysis**

QC samples and standards samples were prepared from a certified buprenorphine solution (1 mg/mL) purchased from Cambridge Isotope Laboratories Inc., Andover, Massachusetts. Along with the unknown biologic samples, QC samples and standards samples covering the expected concentration range were processed. The standard curves for the analytes were obtained by weighted least-squares regression (weighting =  $1/x^2$ ) of the measured peak area ratios analyte/internal standard versus the analyte concentrations added to the plasma. The standard curves were then used to calculate concentrations of the analytes in unknown and QC samples from the measured peak area ratios. QCs were randomized to bracket unknown samples. A Dell PC computer was used for instrument control, data acquisition, and data processing. Data acquisition and integration of SRM chromatograms were performed with the Analyst software package (version 1.4) from AB/MDS Sciex.

#### **Experimental Pain Procedures**

Pain was assessed both subjectively and objectively by means of validated techniques used to explore the peripheral and central nociceptive pathways.

#### **Peripheral Nociceptive Pathways Tested by Thermal Stimulations**

Thermal stimulations were graded to evaluate peripheral thermal perception, then pain thresholds, and finally pain tolerance.

#### **Thermal Perception; Cold and Hot Pain Thresholds**

Thermal thresholds were measured by means of a thermal sensory analyzer (Medoc Advanced Medical

Systems, Ramat-Yishai, Israel), which operates by a microcomputer-driven 3-cm  $\times$  3-cm (9 cm<sup>2</sup>) Peltier contact thermode. The stimulating surface of the thermode was placed in contact with the glabrous skin in the inside of the forearm and secured by a Velcro band. It was heated and cooled within a range of 0°C to 50°C. The gradient of the charge for each stimulation was linear and was set at 1°C/s, with a baseline temperature of 32°C. The cold threshold was assessed first. The perception and pain thresholds were evaluated using the method of limits (mean of 4 measures).<sup>17–20</sup>

#### **Pain Tolerance**

The cold pressor test was used to assess pain tolerance to a tonic, intense pain stimulation.<sup>21–24</sup> This test consists of hand immersion in an ice water bath. A container divided by a mesh screen is filled on 1 side by ice. The ice maintains the water on the other side at  $\sim$ 0°C. A stirring device circulates the water, the temperature of which is monitored by a thermistor with a digital display ( $\pm$ 0.1°C). The mesh screen prevents direct contact between the ice and the skin of the participant.

Participants were instructed to keep their hand in the water until they felt “the maximal bearable pain.” The time until withdrawal of the hand was measured (latency). To avoid causing tissue damage, a cutoff latency was set at 2 minutes.

#### **Central Nociceptive Pathways Tested by Electrical Stimulation**

The nociceptive flexion RIII reflex is considered a specific and objective physiologic correlate of pain sensation.<sup>25–27</sup> Its reliability has been evaluated and found satisfactory by 1 of the authors; this evaluation has been published.<sup>28</sup> Moreover, pharmacologic studies in humans have demonstrated a direct and powerful effect of morphine on the RIII reflex.<sup>26,27</sup> The reflex assesses the central effect of analgesic drugs.<sup>29–31</sup> Because the stimulus is applied directly to the nerve, the peripheral nociceptors are not activated. Briefly, the sural nerve was stimulated in its retromalleolar track using a pair of surface electrodes. The electrical stimulus consisted of single rectangular impulses (0.5 ms) delivered with a 6- to 10-second interstimulus interval by a constant current stimulator at variable intensities (1–100 mA) (Nicolet Viking IV; Nicolet, Madison, Wisconsin). Electromyographic responses were recorded using a pair of surface electrodes placed over

the tendon of the ipsilateral biceps femoris. The RIII reflex (objective threshold) was identified as a multiphasic signal appearing at least 90 ms, but <250 ms, after each stimulation and was considered to be present when the corrected computed surface was >0.5 mV/ms (positive response). After each electrical stimulation, the participants described what they felt using 3 scales: (1) a numeric rating scale from 0 (no pain at all) to 10 (worst pain imaginable), with a cut-off at 4.5 for pain; (2) a sensitive scale with 7 categories (from nothing to very strong pricking or burning sensation); and (3) an affective scale with 7 categories (0 = none to 6 = unbearable).

Objective pain thresholds were then defined as the intensity of current inducing 50% of positive responses to a series of 30 to 40 stimulations, and were obtained by fitting the percentage of positive responses to Hill's equation.

### Psychomotor Measures

Psychomotor performance was assessed by the DSST, a subscale of the Wechsler Adult Intelligence Scale. This test evaluates the ability to concentrate and any modifications in information-processing performance.<sup>32</sup> It is a 1-minute paper-and-pencil test. The participants are required to replace digits with corresponding symbols according to a code given on the same sheet of paper. The score consists of the total number and the correct number of symbols drawn. Different versions of the test (ie, different symbol-digit codes) were used at each assessment. Participants were also asked to rate sedation on a numeric scale from 0 (none) to 10 (severe).

### Adverse Events

The participants were informed about the adverse effects of buprenorphine. They were instructed to report any untoward effects, and adverse events were systematically sought and recorded during the session. The investigators noted the time when the event appeared, its type, seriousness, and duration.

### Data Analysis

Pharmacokinetic parameters were estimated by a compartmental method using WinNonlin version 4.1 (Pharsight Corporation, Mountainview, California). The goodness of fit was checked by comparison of the Akaike and Schwarz criteria. Residuals were also checked for systematic deviations. Pharmacokinetic

parameters such as clearance,  $t_{1/2}$ ,  $C_{max}$ , and distribution volume were calculated from standard equations using WinNonlin.<sup>33</sup> AUC was calculated using the trapezoidal rule. Descriptive statistics were used to summarize the pharmacokinetic data.

Values of peak effect and time to peak were determined directly from the data and expressed as the maximal or minimal difference between the control threshold and the peak value. For the pharmacodynamic measures, we used the nonparametric Wilcoxon signed-rank test for paired data (SPSS for Windows, Version 11.0; SPSS Inc., Chicago, Illinois). Statistical significance was defined as  $P \leq 0.05$ .

## RESULTS

### Study Participants

The participants were 12 healthy male volunteers aged 21 to 34 years (mean [SD], 26 [3.5] years) and weighing 58 to 86 kg (mean [SD], 67 [9] kg). All participants were white. None of the patients had a history of opiate abuse.

### Pharmacokinetics

The mean plasma concentration-versus-time profile of buprenorphine is shown in **Figure 1**. Buprenorphine  $t_{1/2}$  was 2.75 hours. A secondary peak was observed at 90 minutes after buprenorphine administration, suggesting enterohepatic circulation. The individual curves all displayed the same pattern, and a typical example is shown in **Figure 2**. The pharmacokinetic parameters were best described using a 2-compartment model (**Table I**). Adequate fit of the data was evidenced by the high correlation ( $r^2$ , >0.99) between computer-calculated and experimental buprenorphine concentrations.

### Pharmacodynamics

Buprenorphine had no significant effect on thermal perception (data not shown). It was associated with a significant time-related effect on all the other measures (**Figure 3**).

### Nociceptive Tests

At baseline, the mean (SD) RIII reflex threshold and subjective threshold were 31.6 (9.5) mÅ and 45.5 (22.3) mÅ, respectively. Buprenorphine significantly increased both thresholds for >4 hours. The maximum increases (mean [SD]) were +14.1 (17.5) mÅ for the RIII reflex ( $P = 0.02$ ) and +24.2 (21.7) mÅ for the

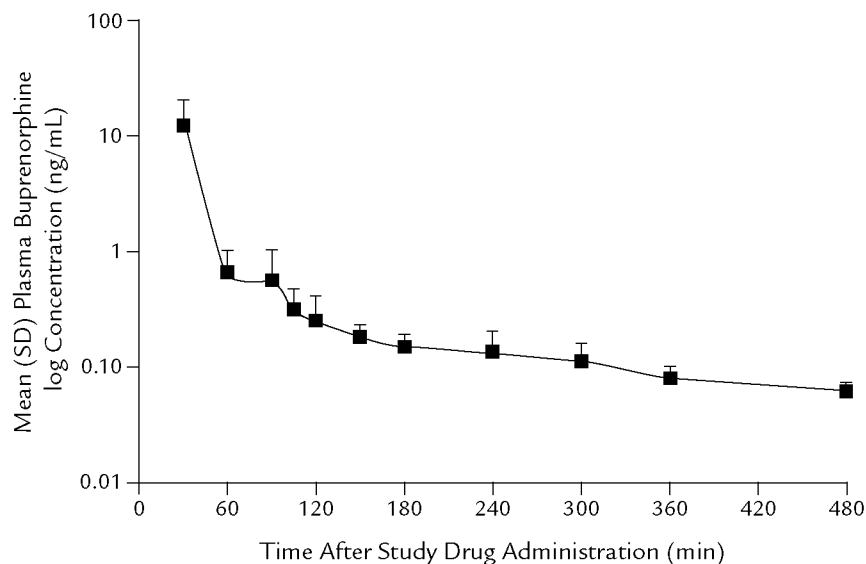


Figure 1. Plasma buprenorphine concentration over time after a single IV dose of 0.002 mg/kg to 12 healthy male volunteers.

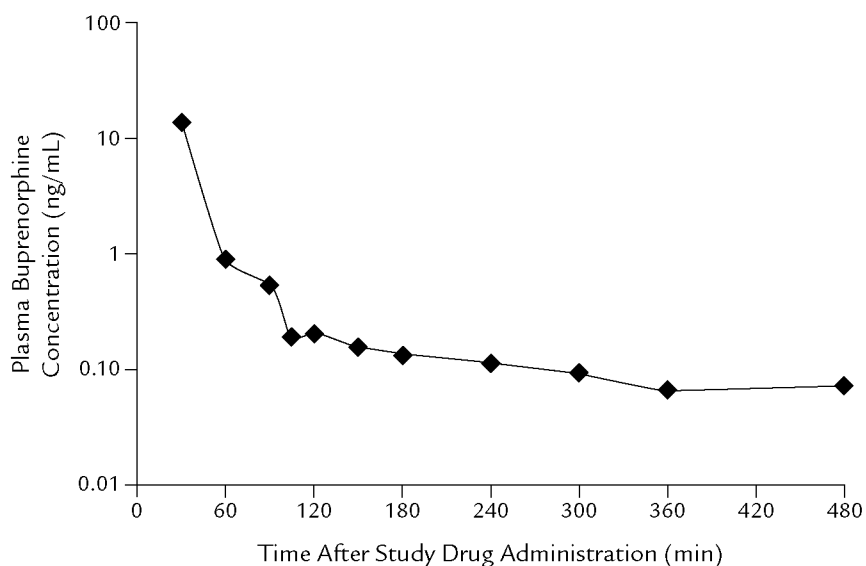


Figure 2. Volunteer 1: Plasma buprenorphine concentration over time after a single IV dose of 0.002 mg/kg (0.15 mg/70 kg).

subjective threshold ( $P = 0.02$ ), corresponding to percentages (mean [SEM]) of 53.7% (20.2%) and 74.7% (20.4%) of the baseline values, respectively. The effect of buprenorphine on pain tolerance (cold pressor test) peaked early ( $T_{\max} = 30$  minutes) and was of shorter duration (2 hours). At  $T_{\max}$ , mean (SEM) latency before withdrawal of the hand was 69 (10) seconds, cor-

responding to a mean (SEM) increase of 63.8% (14.4%) from baseline ( $P = 0.003$ ).

#### **Psychomotor Performance and Sedation**

Buprenorphine significantly impaired psychomotor performance on the DSST. The effect observed was on the total number of symbols, and not on the number

Table I. Estimated pharmacokinetic parameters for buprenorphine after administration of a single IV dose of 0.002 mg/kg to 12 healthy male volunteers. Values are mean (SD).

Parameter	Value
$C_{max}$ , ng/mL	207 (196)
$t_{1/2}$ , h	2.75 (0.64)
CL, mL/h	6807 (4219)
CL/W, kg · mL/h	101.5 (59.8)
AUC, ng · mL/h	34.6 (26.9)
$V_d$ , mL	1598 (1397)
$V_d/W$ , mL/kg	23.3 (18.2)

CL = clearance; CL/W = clearance corrected for body weight;  $V_d$  = volume of distribution;  $V_d/W$  = volume of distribution corrected for body weight.

of symbols drawn correctly. The maximum effect occurred at 1 hour, when the mean total score decreased from 41 to 35 symbols drawn (14.5%;  $P = 0.005$ ). A marked effect was also observed on the ratings of drowsiness. At peak effect, mean scores increased from 2.9 to 6.4 (SEM 0.7) on a 10-point linear scale ( $P = 0.005$ ). Values for both measures had returned to baseline by the end of the session, unlike for the nociceptive tests.

### Adverse Events

All participants completed the study. One or more adverse effects related to buprenorphine were observed, including nausea (9/12; 75%), lightheadedness (8/12; 67%), drowsiness (7/12; 58%), and vomiting (5/12; 42%) (Table II). Most participants ( $n = 8$ ) reported lightheadedness within a few minutes (mean, 10 minutes; range, 3–24 minutes) after the administration of buprenorphine. All of the participants were symptom free at the end of the session.

### DISCUSSION

Our data were collected as part of a study on the efficacy of naltrexone, a pure synthetic opioid antagonist, in reversing the action of buprenorphine. The aim of this substudy was to provide pharmacokinetic data on IV buprenorphine at a clinically relevant analgesic dose of 0.002 mg/kg (0.15 mg/70 kg) in healthy volunteers, together with assessments of analgesic and psychomotor effects.

The LC-MS/MS method we developed quantified buprenorphine plasma concentrations after a single 0.002-mg/kg IV dose and allowed adequate characterization of the terminal phase. Early studies of buprenorphine pharmacokinetics were limited by insufficient assay sensitivity.<sup>34,35</sup> In the most commonly used method, immunoassay, a cross-reaction of the buprenorphine metabolite with the antibody leads to overestimation of the concentrations of buprenorphine.<sup>36</sup> More specific methods have been developed recently using either gas or liquid chromatography coupled to mass spectrometry.<sup>37–39</sup> However, they are not sensitive enough for determination of buprenorphine doses as low as those used to treat pain as their lower limit of quantification is >0.1 ng/mL. This study allowed us to characterize buprenorphine pharmacokinetics and related pharmacodynamics after the administration of a clinically relevant analgesic dose of 0.002 mg/kg.

The  $t_{1/2}$  of 2.75 hours in this study compares well with previously reported values of 3 hours and 3.21 hours in surgical patients and healthy men, respectively.<sup>4,35</sup> A 2-compartment model adequately described buprenorphine pharmacokinetics. Other studies in animals and humans have suggested that a triexponential model fits the concentration-time course best.<sup>35,40–42</sup> The difference may be due to the design of our study, as early measurement points were not present in a sufficient number to show a fast distribution phase. The study design would also explain why the values of some parameters (ie, volume of distribution, clearance) differed between studies. The plasma concentration-time course of buprenorphine showed a secondary peak at 90 minutes, which suggests enterohepatic circulation. Previous studies have reported enterohepatic circulation for buprenorphine in the rat, and evidence for its existence was also found in humans.<sup>10,43,44</sup> The influence of food to explain our findings is unlikely because the volunteers were tested after an overnight fast and were not given a meal until 4 hours after buprenorphine administration.

Buprenorphine had a significant effect on nociception, and the findings were consistent across all the measures assessed. Buprenorphine had a significant effect on pain tolerance ( $P = 0.003$ ) and on the objective and subjective pain thresholds ( $P = 0.02$ ), which involve both spinal and supraspinal pathways. Time to peak effect was 30 and 120 minutes, respectively. The increase in the objective pain threshold was close to the maximal

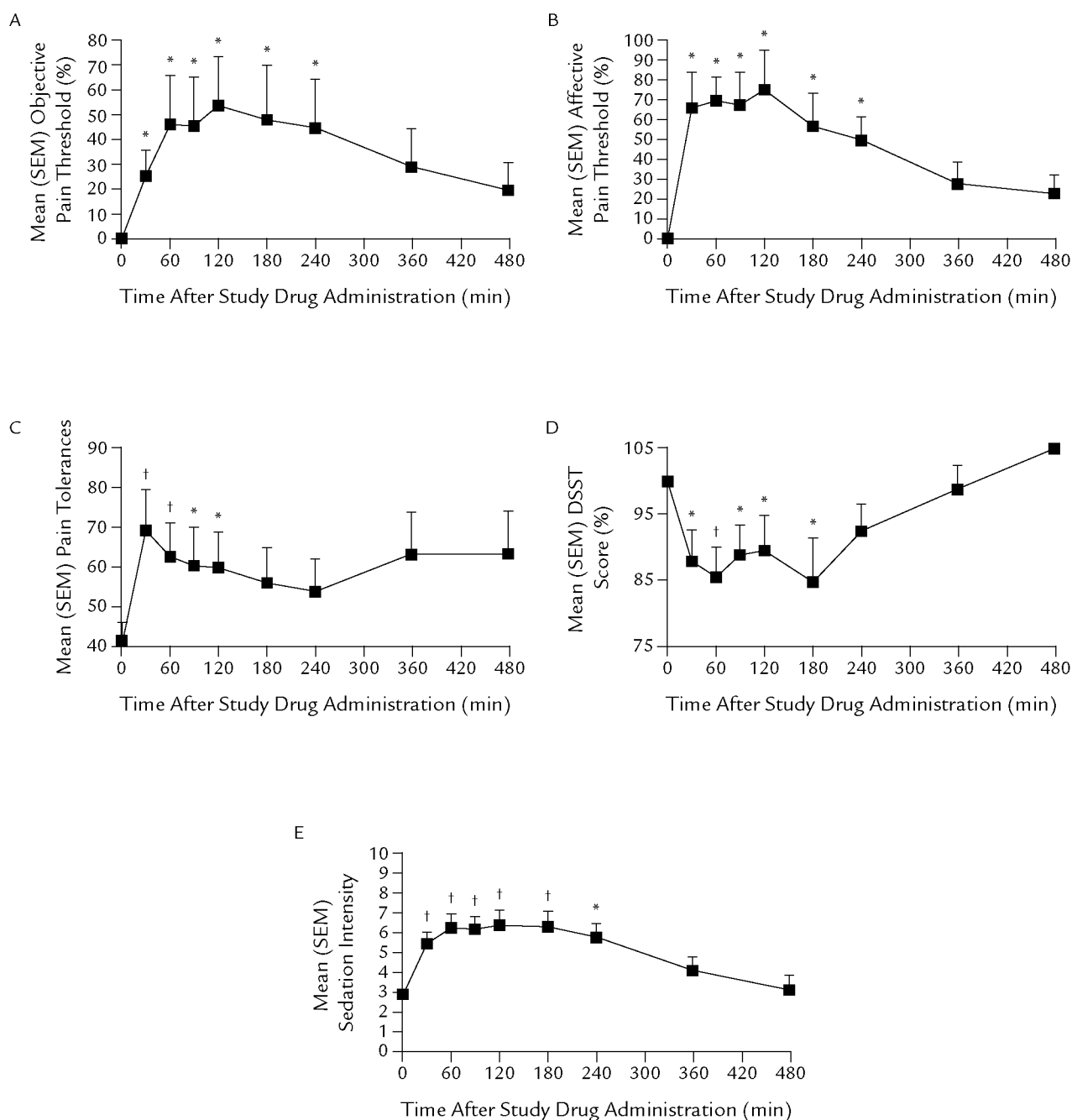


Figure 3. Variations over time in (A) objective pain threshold, as measured using sensory testing with electrical (nociceptive flexion RIII reflex) stimulations; (B) affective pain threshold; (C) pain tolerance, as measured using the cold pressor test; (D) psychomotor performance, as measured using the digit symbol substitution test (DSST); and (E) sedation intensity, as measured on an 11-point scale (0 = none to 10 = severe) in 12 healthy male volunteers after a single IV dose of 0.002 mg/kg buprenorphine. \* $P < 0.05$  versus baseline (nonparametric Wilcoxon signed-rank test); † $P < 0.01$  versus baseline (nonparametric Wilcoxon signed-rank test).

Table II. Adverse events (AEs) after administration of a single IV dose of buprenorphine 0.002 mg/kg in 12 healthy male volunteers.

AE	Total	Mild	Moderate	Severe
Nausea	9	3	5	1
Lightheadedness	8	6	1	1
Drowsiness*	7	1	5	1
Distorted perceptions†	5	2	3	0
Vomiting	5	2	1	2
Difficulty focusing attention	2	1	0	1
Difficulty urinating	2	2	0	0
Fatigue	2	2	0	0
Feeling unsteady	2	2	0	0
Sweating	2	1	1	0
Epigastric cramping	1	1	0	0
Sensitivity to temperature	1	0	1	0
Fullness/bloating	1	0	1	0
Headache	1	0	1	0
Hiccups	1	0	1	0
Itching	1	1	0	0

\*Considered an AE when mentioned by the volunteer independently from the scheduled assessment of sedation.

†Feeling detached, sensation of slurred speech, time distortion, increase in hearing, difficulty focusing; n = 1 for each.

value at 60 minutes. In clinical studies of IV buprenorphine for postoperative pain, effective analgesia was obtained within a similar time frame.<sup>9,45</sup> Maximal pain relief was observed 1 hour after patients with a lower abdominal incision had received a dose of 0.005 mg/kg.<sup>9</sup> In a study in 51 patients who underwent abdominal surgery, a statistically significant decrease in pain scores occurred 30 minutes after the administration of 0.1 to 0.2 mg buprenorphine delivered by a patient-controlled analgesic device.<sup>45</sup>

Our finding that buprenorphine impaired psychomotor performance is concordant with previous results in non-opioid-dependent volunteers.<sup>46</sup> A significant decrease in performance on the DSST was reported for doses ranging from 0.075 mg/70 kg to 0.3 mg/70 kg compared with placebo.<sup>46</sup> Both measures on the DSST (ie, number completed and number correct) were affected. In our study, no effect was observed on the number of correct symbols drawn. A slowing of performance rather than a decrease in accuracy seemed to occur with lower doses of opioids.<sup>46,47</sup> Moreover, the different setting of the experiments may explain this finding.

Sedation is a dose-dependent, primary subjective effect reported by volunteers given buprenorphine.<sup>46,48</sup>

Although a low dose was administered, our participants experienced a high level of drowsiness, with a mean peak increase of 3.5 points on a 10-point linear scale. Drowsiness occurred rapidly and lasted for about 3.5 hours.

The onset of buprenorphine effects occurred during the distribution phase for all measures. Peak effects were observed during the distribution phase for pain tolerance, psychomotor performance, and sedation. The changes in values compared with baseline remained statistically significant for 120 to 240 minutes after drug administration ( $P < 0.05$ ), hence across a wide range of concentrations during the elimination phase. The most likely explanation for this finding is the high affinity of buprenorphine at  $\mu$ -opioid receptors. According to recent data, distribution to the brain might also contribute significantly to the onset and offset of its antinociceptive effects.<sup>41,42</sup>

Our study has several limitations. A single dose was administered. Multiple dosing would allow us to more fully determine buprenorphine pharmacokinetics and pharmacodynamics. All the participants were men. Sex differences in the perception and modulation of pain have been described.<sup>49</sup> More specifically, women were found to have lower nociceptive flexion RIII reflex

thresholds than men.<sup>50</sup> Therefore, the extent of buprenorphine's effects on nociception in women cannot be inferred from our results. Drug pharmacokinetics and pharmacodynamics can change with age. For example, adults aged >60 years, compared with younger adults, experienced more significant respiratory depression after the administration of 75 µg remifentanyl.<sup>51</sup> The mean age of the volunteers in our study was 26 years, and the findings cannot be generalized to older adults.

## CONCLUSIONS

A clinically relevant, low dose of buprenorphine (0.15 mg for a 70-kg man) was found to have analgesic effects in these healthy adult male volunteers as measured by means of validated techniques. After a single administration, a decrease in psychomotor performance and marked sedation were observed. The effect of buprenorphine was statistically significant on all the measures at 30 minutes and then lasted between 90 minutes for pain tolerance and 210 minutes for objective and subjective pain thresholds and sedation. A 2-compartment model satisfactorily characterized buprenorphine pharmacokinetics, and we found evidence of enterohepatic circulation. The pharmacokinetic behavior of buprenorphine, especially during the distribution phase, must be studied further in patients (as opposed to healthy volunteers). Issues such as variability according to age, sex, and ethnicity should be addressed.

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