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Pharmacokinetic Evaluation of a Topical Extended-Release Analgesic in Mice

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Mice often undergo painful procedures and surgeries as part of biomedical research protocols. Buprenorphine, a partial μ-opioid receptor agonist and κ receptor antagonist, is commonly used to alleviate the pain associated with such procedures. Due to its pharmacokinetic profile, buprenorphine requires frequent dosing, resulting in handling stress that can impact animal welfare and study data. A long-acting transdermal buprenorphine formulation (LA-bup) was recently approved for use in cats to provide up to 4 d of postoperative analgesia. In this study, we characterized the pharmacokinetics of a single topical dosing of LA-bup in male and female CD-1 mice administered a 0.36-mg or 18-μL topical dose at select time points. Plasma buprenorphine concentrations were evaluated at 0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 48, and 72 h (*n* = 3 mice/time point) and remained above the purported therapeutic threshold (1 ng/mL) from 1 to 24 h postadministration. Repeated daily dosing at 24 and 48 h demonstrated plasma levels above 1 ng/mL for up to 72 h with minimal accumulation or changes in maximal concentrations over time. Inadvertent transfer of the topical drug to nondosed mice in the same cage was evaluated by measuring plasma buprenorphine concentrations in nondosed mice cohoused with a single-dosed mouse. Male mice did not demonstrate transfer of drug via grooming or interactions, yet 2 out of 26 nondosed female mice had detectable buprenorphine plasma levels indicating a relatively low incidence of cross-ingestion in cohoused female mice. This study demonstrates that LA-bup is a promising analgesic in mice that could be used for tailored analgesia strategies, depending on the surgical model or duration of analgesic therapy.

Abbreviations and Acronyms: bup-HCl, buprenorphine-hydrochloride; LA-bup, long-acting transdermal buprenorphine formulation

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Introduction

The prevention and alleviation of pain in laboratory animals are integral to ensuring animal welfare, generating quality scientific data, and maintaining regulatory compliance. Mice, one of the most used laboratory animal species, often undergo painful procedures and surgeries, making analgesic refinement in this species an important area of research. Commonly used analgesics in mice include NSAIDs, such as carprofen, local anesthetics such as lidocaine, and opioids such as buprenorphine. Depending on the procedure performed, one to several days of postoperative analgesia may be needed to manage pain and maintain appropriate animal welfare. Based on the pharmacokinetic profiles for commonly used nonsustained-release analgesics, multiple injections per day are generally necessary to maintain therapeutic analgesic plasma levels during the postoperative time period.[8] This increases handling-associated stress in the animals and the potential for breakthrough pain and confounded experimental data if analgesic levels rapidly drop between dosing intervals.[1,2,11,23]

Buprenorphine-HCl (bup-HCl) is a high-affinity partial μ-opioid receptor agonist with a slow rate of receptor dissociation as well as a κ receptor antagonist.[4,5,14] It is a widely used analgesic in mice and is generally considered an ideal choice for control of moderate to severe pain secondary to surgery, clinical, or experimental procedures. Traditionally, bup-HCl was dosed every 12 h when administered subcutaneously to mice; however, recent pharmacokinetic studies have found that plasma concentrations likely drop below the purported minimum therapeutic level (1 ng/mL) anywhere between 4 and 6 h after administration.[13,17,18] As a result, long-acting or sustained-release products have been evaluated for use in mice.[15,18] Several FDA-indexed or FDA-approved extended-release analgesic drugs have become available in recent years as alternatives to bup-HCl, including Ethiqa-XR (indexed for mice, rats, and ferrets), Simbadol (approved for cats), and, most recently, a novel transdermal formulation of buprenorphine, Zorbium (LA-bup; approved for cats). In mice, the pharmacokinetics of Simbadol are similar to that of high-dose bup-HCl, precluding its use as an extended-release analgesic in this species.[19,24] Several studies have been conducted evaluating the pharmacokinetics and clinical efficacy of Ethiqa-XR in mice and rats, concluding that it provides 48 to 72 h of analgesia after a single subcutaneous injection.[3,16,21] However, the use of Ethiqa-XR by investigators may be hampered by its cost and limited in use life postbroaching (90 d after vial broached).

A transdermal extended-release buprenorphine formulation, LA-bup, was approved in 2022 for up to 4 d of postoperative pain control in cats.[6,9] The medication is applied topically between the shoulder blades in cats eliminating the need for, or potential stress associated with, parenteral injections. One study evaluated the use of LA-bup, in female C57BL/6

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mice using doses of 30 and 40 mg/kg topically, which demonstrated plasma concentration exceeding the purported therapeutic threshold (1 ng/mL) for up to 72 h (30 mg/kg) and 96 h (40 mg/kg).[7] Results from this study demonstrate an exciting potential alternative due to the topical route of administration, affordable cost, and reduced animal handling requirements compared with parenteral administration.

In this study, we sought to evaluate the pharmacokinetics of LA-bup in mice over a 72-h period using a lower dose than previously published and in male and female outbred CD-1 mice. The study had 3 objectives: 1) to evaluate the pharmacokinetics of LA-bup in outbred male and female CD-1 mice for up to 72 h after a single administration; 2) to analyze the effects of once-daily LA-bup administration on plasma concentrations over a 72-h period; and 3) to evaluate the potential for inadvertent ingestion or exposure of clinically relevant amounts of LA-bup among cage mates through contact or grooming. In addition, we hypothesized the following: that a lower single dose of LA-bup could be dosed daily providing additional options for tailoring analgesia therapy and minimizing adverse or confounding effects; peak or prolonged buprenorphine plasma concentrations would be minimally affected by serial daily dosing; and minimal exposure of LA-bup would occur via direct contact with cohoused mice or allogrooming.

Materials and Methods

Animals. Eight to 10-wk-old male and female CD-1 mice were ordered from Charles River Breeding Laboratories. They were designated SPF for mouse hepatitis virus, minute virus of mice, mouse parvovirus, epizootic diarrhea of infant mice virus, ectromelia virus, Sendai virus, pneumonia virus of mice, Theiler murine encephalitis virus, reovirus, lymphocytic choriomeningitis virus, mouse adenovirus, polyomavirus, *Mycoplasma pulmonis*, and pinworms. Mice were housed in microisolation cages (model MBS75JRHMV; Allentown, Allentown, NJ) on corncob bedding (The Andersons Plant Nutrient, Webberville, MI) in ventilated racks under constant environmental conditions (68 to 72 °F [20 to 22.2 °C], 30% to 50% relative humidity, 12:12-h light:dark cycle). Mice were provided with rodent chow (Laboratory Rodent Diet 5001; PMI LabDiet, St. Louis, MO) and reverse osmosis water ad libitum. Mice were housed in same-sex groups of 3 individuals per cage throughout the duration of the study. All procedures were performed at an AAALAC International-accredited facility and with the approval of the University of Michigan Institutional Animal Care and Use Committee in accordance with the *Guide for the Care and Use of Laboratory Animals.*

Buprenorphine. LA-bup (Zorbium; Elanco Animal Health Incorporated, Greenfield, IN) was obtained as 0.4-mL tubes at a concentration of 20 mg/mL. Allometric scaling was used to determine a mouse dose range of 9 to 18 mg/kg based on the cat dose range of 2.7 to 6.7 mg/kg.

Single-dose pharmacokinetic study. Male and female CD-1 mice were allocated to one of 10 time points (0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 48, and 72 h after injection, $n = 3$ males and 3 females per time point; see Figure 1). Mice were briefly anesthetized with isoflurane to facilitate accurate LA-bup application directly onto the skin. After the mice were anesthetized, they were placed in sternal recumbency and the fur was parted on the nape of their necks per label recommendations. The contents of one 0.4-mL tube of LA-bup were emptied into a sterile screw cap microcentrifuge tube, and a 20-µL pipette was used to draw up and apply 0.36 mg (18 µL) of LA-bup directly onto the skin in the area of fur parting. Mice were placed individually into

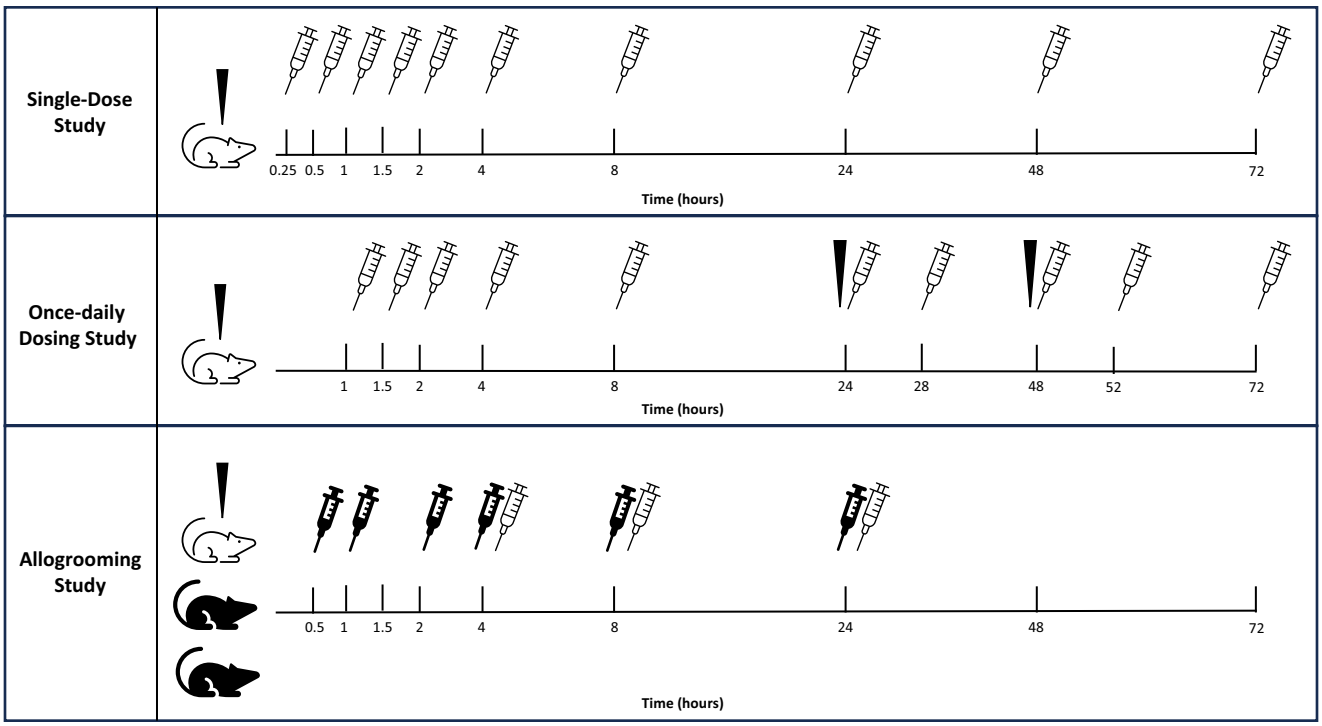

Figure 1. Study design for the single-dose, once-daily dosing, and allogrooming studies. Open mouse = dosed mouse; filled mouse = naïve mouse; arrowhead = LA-bup dosing; open syringe = blood collection from dosed mouse; filled syringe = blood collection from naïve mouse. For single-dose and once-daily dosing studies, $n = 3$ male and 3 female mice per time point. For the allogrooming study, mice were kept in cages of 1 dosed and 2 naïve mice of the same sex ($n = 1$ male and 1 female cage for the 0.5-, 1-, 2-, and 4-h time points and 2 female cages for the 8- and 24-h time points). In the allogrooming study, blood collection from naïve mice took place at their group's assigned time point. Blood collection from dosed mice in the allogrooming study took place at 4 h for the 0.5-, 1-, 2-, and 4-h groups and at their group's assigned time point for the 8- and 24-h groups.

clean, bedded cages for 30 min after application to allow time for anesthetic recovery and initial LA-bup absorption before being returned to their home cages. At their designated time points, mice were deeply anesthetized with isoflurane, and terminal blood collection was performed via cardiac puncture. Approximately 0.5 to 0.7 mL of blood was collected, placed into EDTA microtainers, and then centrifuged at 4 °C and 4 × *g* for 10 min. Plasma was separated and aliquoted into microfuge tubes for storage at −80 °C. Pharmacokinetic analysis was performed by liquid chromatography-mass spectrometry at the Pharmacokinetic and Mass Spectrometry Core, Department of Pharmacy, University of Michigan (Ann Arbor, MI). The limit of quantification was 1 ng/mL.

Daily dosing pharmacokinetic study. Male and female CD-1 mice were allocated to one of 10 time points (1, 1.5, 2, 4, 8, 24, 28, 48, 52, and 72 h after injection, n = 3 males and 3 females per time point). Time points at 28 and 52 h were included to approximate an estimated maximum time (T_{max}) of 4 h after the second and third doses (Figure 1). Buprenorphine (0.36 mg = 18 µL) was administered topically at 0, 24, and 48 h. Administration procedures and blood collection methodology were similar to the single-dose pharmacokinetic study.

Allogrooming study. Mice were housed in groups of 3 same-sex individuals with one mouse per group being dosed with LA-bup (Figure 1). Administration procedures were as described above; however, the mice were returned to their home cages immediately after recovery from anesthesia instead of being housed individually for 30 min. Pharmacokinetic analysis time points for nondosed cagemates were 0.5, 1, 2, 4, 8, and 24 h. Blood was collected from the nondosed mice via terminal cardiac puncture at their assigned time point. The dosed mice in cages for these time points (0.5, 1, 2, and 4 h) were collected for terminal cardiac puncture at 4 h postadministration to estimate peak plasma concentration. The dosed mice for the 8- and 24-h time points were collected at the same assigned time points as the nondosed mice so that the nondosed mice would be exposed to the dosed mice for the entirety of their postdosing interval. Data after 4 h could not be collected in male mice due to unexpected separation for fighting.

Statistical analysis. Data was analyzed using GraphPad Prism software (Prism 9; GraphPad Software, La Jolla, CA). Body weight distributions, dose, and mean plasma concentrations per time point were summarized as mean ± 1 SD by using GraphPad Prism software (Prism 9; GraphPad Software, La Jolla, CA). Noncompartmental pharmacokinetic parameters were estimated with Phoenix/WINONLIN (Certara, Princeton, NJ). $AUC_{0\text{-max}}$ was defined as the AUC from time 0 to time of maximum concentration, $AUC_{0\text{-inf}}$ was defined as the AUC from time zero to infinity, and terminal elimination half-life ($t_{1/2}$) was calculated based on data points in the terminal phase. The linear trapezoidal rule was used for the area under the concentration-time curve (AUC) calculation. Clearance and volume of distribution parameters were not included in noncompartmental pharmacokinetic analysis due to the topical route of administration and the need for advanced pharmacokinetic modeling. A Student *t* test was used to perform statistical analysis between male and female mice at each pharmacokinetic time point. A *P* value less than 5% was considered a significant difference. A minimum of 3 animals per group would be required for similar studies to detect a ≥50% effect size difference between male and female mice using the topical buprenorphine doses evaluated in the first pharmacokinetic study, plasma concentrations >1 ng/ml , and AUC0–24 h with 80% power and a two-sided significance level of 5%. This is based on a mean AUC0–24 h of 67.14 ng*h/ml (SE ± 15.14) in male mice. If comparing different formulations for bioequivalence or 20% difference such studies would require 20 animals per group. Data analysis was performed using GraphPad Prism software (Prism 9; GraphPad Software, La Jolla, CA).

Table 1. Single-dose pharmacokinetic noncompartmental analysis estimated for female and male CD-1 mice

	$AUC_{0\text{-}Tmax}$ (ng·h/mL)	$AUC_{0\text{-inf}}$ (ng·h/mL)	C_{max} (ng/mL)	Half-life (h)
Females				
Mean	51.8	75.8	11.9	12.3
SD	30.9	37.6	8.1	9.3
Males				
Mean	66.0	93.0	6.1	19.2
SD	36.0	54.8	0.9	17.5

Mean dose = 11.8 mg/kg for females and 8.6 mg/kg for males (18 µL topically).

Results

Single-dose pharmacokinetic study. This study used a standard dose of 18 µL administered topically, which correlates to 0.36 mg of buprenorphine (20 mg/mL). For the single-dose pharmacokinetic study, the mean ± SD weight (g) of male and female mice was 42.2 ± 3.0 and 30.6 ± 2.1, respectively. This correlated to a dose (mg/kg) for male and female mice (mean ± SD) of 8.62 ± 0.65 and 11.8 ± 0.82, respectively. Plasma concentrations for a single dose of topical buprenorphine were obtained in male and female CD-1 mice over a 72-h time period (n = 3 mice per time point). A noncompartmental pharmacokinetic analysis (mean ± SD) for CD-1 male mice demonstrated a maximum concentration (C_{max}; ng/mL) of 6.12 ± 0.91, $AUC_{0\text{-}Tmax}$ (ng·h/mL) of 65.96 ± 35.99, AUC0-inf (ng·h/mL) of 92.99 ± 54.83, and a half-life (h) of 19.19 ± 17.50 (see Table 1). A noncompartmental pharmacokinetic analysis (mean ± SD) for CD-1 female mice demonstrated a C_{max} (ng/mL) of 11.93 ± 8.06, $AUC_{0\text{-}Tmax}$ (ng·h/mL) of 51.80 ± 30.89, $AUC_{0\text{-inf}}$ (ng·h/mL) of 75.8 ± 37.61, and a half-life (h) of 12.32 ± 9.26 (see Table 1). Buprenorphine plasma concentration per time profiles for male and female mice are demonstrated in Figure 2. Buprenorphine plasma concentrations were below the level of quantification for the 0.25- and

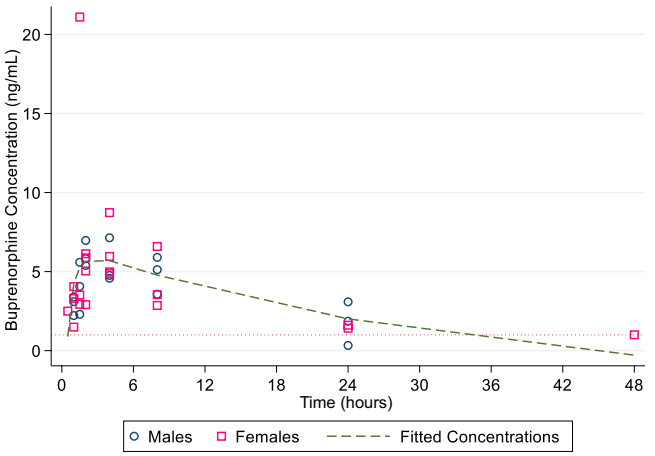

Figure 2. Single-dose concentration-time profile for male and female CD-1 mice. Therapeutic reference line is at 1 ng/mL. Dotted line is noncompartmental plasma concentration per time model. Mice received a single 0.36-mg dose (18 µL) topically. Only data out to 48 h after application are shown as all samples were below the limit of quantification after this point.

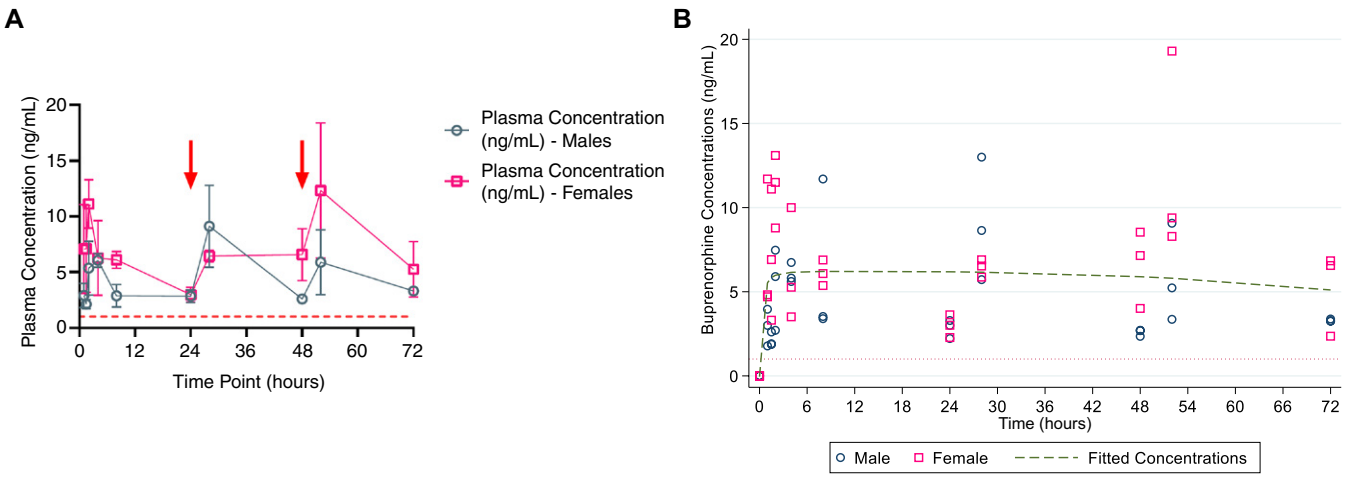

Figure 3. (A) Repeated-dose (24 and 48 h) pharmacokinetic profiles for male and female outbred CD-1 mice. Minimum therapeutic threshold is represented by the dashed line at 1 ng/mL. Arrows indicate repeated daily doses at 24 and 48 h. Data were only collected from male mice up to 4 h due to fighting in a subset of male cages. (B) Repeated-dose (24 and 48 h) concentration profile for male and female CD-1 mice. Therapeutic reference line is at 1 ng/mL. Dotted line is a noncompartmental plasma concentration per time model. Mice received a 0.36-mg dose (18 µL) topically at 0, 24, and 48 h.

0.5-h time points, except one female mouse who demonstrated a plasma level of 2.5 ng/mL at the 0.5-h time point. All mice demonstrated plasma concentrations >1 ng/mL at 1 h. Plasma buprenorphine concentrations were below the limit of quantification in all mice at 48 and 72 h after application. There were no significant differences between male and female mice regarding $AUC_{0\text{-}Tmax}$, C_{max}, or plasma concentrations at any of the time points.

Once-daily dosing pharmacokinetic study. For the daily topical dosing of buprenorphine (0, 24, and 48 h) pharmacokinetic study, the mean ± SD weight (g) of male and female mice was 36.8 ± 2.7 and 27.1 ± 2.9, respectively. This correlated to a dose (mg/kg) for male and female mice (mean ± SD) of 9.8 ± 0.74 and 13.42 ± 1.5, respectively. Mean plasma buprenorphine concentrations remained above the minimum therapeutic threshold (1 ng/mL) at all time points, closely following the plasma concentration over time profiles seen in the single-dose study during the first 24 h (Figure 3). Plasma buprenorphine concentrations were also measured at 28 and 52 h to capture the peak plasma concentrations after the second and third dose administrations (see Figure 3). A noncompartmental pharmacokinetic analysis (mean ± SD) for CD-1 male mice demonstrated a C_{max} (ng/mL) of 11.3 ± 2.0, $AUC_{0\text{-}Tmax}$ (ng·h/mL) of 439.9 ± 39.4, $AUC_{0\text{-inf}}$ (ng·h/mL) of 4,610.9 ± 5,420.8, and a half-life (h) of 62.1 (see Table 2). A noncompartmental pharmacokinetic analysis (mean ± SD) for CD-1 female mice demonstrated a C_{max} (ng/mL) of 14.2 ± 4.4, $AUC_{0\text{-}Tmax}$ (ng·h/mL) of 498.1 ± 44.7, $AUC_{0\text{-inf}}$ (ng·h/mL) of 926.2 ± 353.7, and a half-life (h) of 36.8 ± 16.4 (see Table 2). Mean plasma concentrations (ng/mL) at 1 h for male and female CD-1 mice were 2.91 ± 1.09 and 7.07 ± 4.0, respectively. Based on pharmacokinetic modeling and slope of concentrations at the last time points, the half-life estimates in male mice were not well qualified (including SD), leading the $AUC_{t\text{-inf}}$ to be less reliable than the $AUC_{0\text{-}Tmax}$. There were no significant differences between male and female mice regarding $AUC_{0\text{-}Tmax}$, C_{max}, or plasma concentrations at any time point.

Table 2. Repeated-dose (24 and 48 h) pharmacokinetic noncompartmental analysis estimated for female and male CD-1 mice

	$AUC_{0\text{-}Tmax}$ (ng·h/mL)	$AUC_{0\text{-inf}}$ (ng·h/mL)	C_{max} (ng/mL)	Half-life (h)
Females				
Mean	498.1	926.2	14.2	36.8
SD	44.7	353.7	4.4	16.4
Males				
Mean	439.9	4,610.9	11.3	62.1
SD	39.4	5,420.8	2.0	

Mean dose = 13.4 mg/kg for females and 9.8 mg/kg for males (18 µL topically).

Allogrooming study. The mean ± SD weight (g) of male and female mice was 37.1 ± 2.3 and 26.2 ± 3.1, respectively. This correlated to a mean dose ± SD (mg/kg) in male and female mice of 9.3 ± 0.9 and 13.0 ± 1.6, respectively. No cohoused, nondosed male mice had plasma buprenorphine concentrations above the limit of quantification. Two out of the 4 nondosed female mice in the 8-h group had plasma concentrations above the minimum therapeutic threshold (2.26 and 1.59 ng/mL). The plasma concentrations mean ± SD (ng/mL) of the dosed male and female mice at 4 h were 4.54 ± 2.15 and 5.63 ± 2.83, respectively. At 8 h, the plasma concentration (ng/mL) of the dosed female mice remained stable at 4.31 ± 2.37. By 24 h, the plasma concentration (ng/mL) of the dosed female mice was 2.285 ± 1.252 (see Figure 4).

Discussion

These results demonstrate that LA-bup, a topical, extended-release formulation of buprenorphine, achieves therapeutic plasma concentrations (1 ng/mL) within 1 h and lasts up to 24 h after application when given at the studied dose range to CD-1 mice. Furthermore, the results indicate that repeated daily dosing of LA-bup can be used to maintain therapeutic plasma concentrations for greater than 24 h with minimal accumulation. The noncompartmental analysis model further suggests that once-daily dosing of LA-bup can create a sustained-release type pharmacokinetic profile. When administered to mice approximately 1 h before surgery or other painful procedures, LA-bup could be used for preemptive analgesia protocols. A recently published study using a significantly higher dose of LA-bup (40 mg/kg) found that mice maintained therapeutic plasma concentrations from 2 to 96 h after administration.[7] Taken together, the results from this study and the previous publication demonstrate that the therapeutic duration of LA-bup is likely dose dependent. As the dose used in

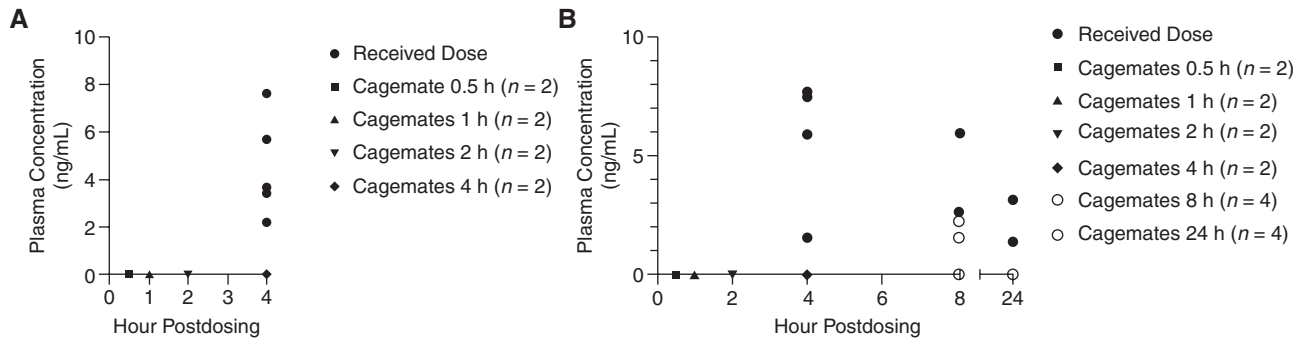

Figure 4. Buprenorphine plasma concentrations at designated time intervals. (A) Male CD-1 mice, one mouse dosed per cage. (B) Female CD-1 mice, one mouse dosed per cage.

this study provided therapeutic plasma concentrations for 24 h and the dose used by another study, provided 96 h, it is possible that use of an intermediate dose could tailor the duration of therapeutic plasma concentration.[7] This provides enhanced dosing flexibility in analgesic protocols depending on the duration of analgesia needed and the dose used.

This study used a standard dose of 18 µL administered topically, which correlates to 0.36 mg of buprenorphine (20 mg/mL) and was within our estimated allometric range for the majority of our mice (9 to 18 mg/kg) based on the labeled dose for use in cats. The dose range varied due to differences in body weights for male and female CD-1 mice with some of the heavier males receiving doses slightly below the calculated dose range. Despite this, all male mice still achieved therapeutic plasma concentrations following the same pattern as the mice dosed within the calculated range. The estimated cost for a 0.4 mL vial of LA-bup is approximately $10.00, which correlates to an estimated cost of $0.50 per mouse per day with approximately 22 doses per vial. Conversely, at the current cost for our institution, an FDA-indexed, extended-release alternative is approximately $10.40 per dose. Actual doses per vial may vary due to loss of drug via pipette manipulations and other factors such as price fluctuations, yet the cost per mouse is generally less than that with currently available sustained-release compounded or FDA-indexed products.

The C_{max} in this study was reported at approximately 4 to 8 h, which is similar to findings in C57BL/6 mice.[7] The ability to use a lower dose and thus lower peak plasma concentrations may reduce the potential for adverse clinical or confounding effects such as hyperactivity, disruptions in circadian rhythm, sedation, and weight loss if those effects are dose dependent.[8,17] While they were not specifically investigated in this study, no adverse clinical effects were noted in the dosed mice, consistent with the current literature on the use of LA-bup in mice.[7]

This study also investigated the potential for ingestion or exposure of LA-bup through direct contact or conspecific allogrooming. The results indicate that there is a chance of contact exposure to LA-bup among cage mates, particularly among female mice. The lower average body weight of the female mice in this study compared with that of the males may have played a role in this due to body surface area variances. Sex differences in affiliative behaviors may have contributed as well. The literature characterizing affiliative behavior in mice is variable. For example, one group found that female CD-1 mice spent less time engaged in social grooming than did males.[22] Conversely, another study investigating pain-related social behavior in mice found that female mice exhibited increased approach behavior to same-sex conspecifics when they were showing signs of pain.[20] Perhaps stress associated with handling could have a similar effect. Allogrooming behaviors have also been shown to vary depending on age and strain of mice, suggesting that the degree of conspecific LA-bup ingestion may vary based on a variety of factors.[25] The LA-bup package insert recommends avoidance of direct contact with the area of application for 30 min postapplication.[6] Based on this recommendation, an investigator or clinician concerned about inadvertent LA-bup exposure between mice, may consider incorporating a 30-min period of separation from cage mates after administration.

The potential synergistic benefits to the welfare of avoiding injections and aversive handling techniques while providing long-acting pain relief make LA-bup an especially attractive option in mice. Other long-acting buprenorphine formulations require restraint and injections, both of which are shown to be stressful in mice.[12] In fact, aversive handling and restraint methods in mice can act as experimental confounds and reduce voluntary interaction between mice and humans.[10,12,27] In this study, we used brief isoflurane anesthesia for dosing to ensure accuracy; however, a previously published study shows that awake mice can be successfully dosed via a pipette.[7] Future studies validating the use of less aversive handling methods such as placing mice in cupped hands or briefly lifting them onto cage enrichment for LA-bup dosing would help maximize the welfare benefits of LA-bup.[26]

In conclusion, this study demonstrates that LA-bup is a promising alternative to bup-HCl and other extended-release buprenorphine-approved formulations for use in mice. Further studies incorporating surgical behavioral models or evoked reflexive pain assays to investigate efficacy are warranted. In addition, pharmacokinetic studies in rats may also demonstrate therapeutic plasma concentrations to support its use as an analgesic in this species. If found effective, LA-bup would be beneficial to animal welfare through decreased aversive restraint such as scruffing and a less invasive route of administration when compared with the parenteral injections required for other buprenorphine formulations. Furthermore, it would provide an affordable alternative to other extended-release formulations with increased dosing flexibility or the ability to tailor analgesic duration in the development of analgesic protocols.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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