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Pharmacokinetic Profiles of a New Extended-release Buprenorphine Formulation in Cynomolgus Macaques (*Macaca fascicularis*)

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The primary objective of this study was to evaluate the pharmacokinetic profile of a new extended-release formulation of buprenorphine (BupBaseER) at a dose that would produce pain management of the desired duration. A secondary objective was to compare the incidence of injection site reactions between the original extended-release formulation (BupHClER) and BupBaseER, which uses a different proprietary polymer-based vehicle than does the BupHClER formulation. Eighteen cynomolgus macaques (*M. fascicularis*) were divided into 2 groups. Each macaque in the first group (*n* = 6) received a single subcutaneous injection of 0.06 mg/kg BupBaseER (10 mg/mL) followed at least 2 wk later by a single subcutaneous injection of 0.12 mg/kg. Animals in group 2 (*n* = 12) received 2 injections of each of 3 compounds—the original polymer matrix vehicle used in BupHClER, the modified polymer matrix vehicle used in BupBaseER, and 0.9% saline—in designated areas of the dorsoscapular region. The 0.06- and 0.12-mg/kg doses both maintained therapeutic levels that were 3 times higher than the hypothesized analgesic threshold of 0.1 ng/mL. These doses maintained therapeutic level for approximately 44 and 103 h, respectively. Based on these data, buprenorphine concentration likely remains well above the therapeutic threshold beyond the 120 h span of this study. During the 30 d after administration, one macaque had a mild skin reaction to BupHClER. None of the animals in either group had skin reactions to BupBaseER at either dosage. These findings support the use of BupBaseER to provide pain management, promote animal welfare, decrease animal stress, and simplify the postoperative management of NHP in research and zoological settings.

Abbreviations: BupBaseER, buprenorphine base extended-release (new formulation); BupHClER, buprenorphine HCl extended-release (original formulation); HDB, high-dose BupBaseER; LDB, low-dose BupBaseER

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Introduction

Buprenorphine's widespread use in veterinary medicine is attributed to its favorable safety profile as compared with other available opioid agents. Considerable published data on the efficacy and recommended dosage of buprenorphine are available for various species, including mice, rats, rabbits, cats, dogs, NHP, and pigs.[1,7,14,21,25,26,30,33,36,40]

Buprenorphine is a semisynthetic lipophilic opioid derived from oripavine and is classified as a μ-opioid receptor partial agonist and a κ-opioid receptor antagonist, with approximately 25 to 40 times the potency of morphine.[8,24] Buprenorphine has a wide safety margin due to its ability to partially bind to the μ-receptor and thus create a ceiling effect, such that increasing the dose does not increase adverse effects.[41] However, a limiting factor of many analgesics, including opioids, is a relatively short duration of action. Buprenorphine has a longer half-life than other opioids, but the duration during which plasma levels exceed the putative therapeutic threshold of 0.1 ng/mL ranges between 6 and 12 h.[19,26,33,37]

Although the therapeutic threshold of buprenorphine in macaques has not yet been established, several studies have cited 0.1 ng/mL as the absolute minimal potential therapeutic threshold. In comparison, a targeted therapeutic plasma buprenorphine concentration range (0.1 to 0.5 ng/mL) has been suggested for humans, in light of correlations between pharmacokinetic studies applying mass spectrometric methodologies and clinical assessment of subjects with postoperative or chronic pain and analgesiometric assays.[11,12,38] Similarly, a therapeutic buprenorphine concentration of 0.1 ng/mL in dogs has been identified by using mass spectrometry method to control postoperative pain after ovariohysterectomy.[27]

Despite the wide usage of buprenorphine in NHP, relatively little literature on the dosage and frequency of administration is available. In 2013, a single 0.2 mg/kg SC injection of the original extended-release formulation (BupHClER; ZooPharm, Fort Collins, CO) was reported to achieve a plasma concentration above the therapeutic threshold of 0.1 ng/mL for as long as 120 h in rhesus and cynomolgus macaques.[33] In 2019, single injections of 0.24 and 0.72 mg/kg SC of a highly concentrated buprenorphine solution (Simbadol, Zoetis, Kalamazoo, MI) significantly exceeded the therapeutic threshold of 0.1 ng/mL for 48 and 72 h, respectively.[31] In a study that examined the pharmacokinetics

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of a new extended-release formulation of buprenorphine (BupBaseER) in adult marmosets, the plasma concentrations of buprenorphine remained above the 0.1 ng/mL threshold until the final 72-h assay time point.[14]

These longer-acting opioids have the advantage of reduced handling and the number of injections per animal. These drugs also have the potential to improve animal welfare by reducing the number of injections needed over 24 h to ensure analgesia coverage and avoid peaks and troughs in plasma levels that can allow pain to emerge. The long duration of action, low risk of respiratory depression and negligible cardiovascular effects in healthy animals make extended-release buprenorphine an advantageous opioid analgesic agent.[35]

The objective of the current study was to evaluate the pharmacokinetic profile of the lowest effective dose required to achieve putative therapeutic concentration of 0.1 ng/mL for the desired duration of time when administering BupBaseER (10 mg/mL; ZooPharm) as a single subcutaneous dose to macaque species (*Macaca fascicularis*). We hypothesized that BupBaseER would reach and maintain therapeutic levels when administered at both a low dose (LDB; 0.06 mg/kg) and high dose (HDB; 0.12 mg/kg) for at least 24 and 48 h, respectively. The doses for BupBaseER (0.06 and 0.12 mg/kg) were calculated with regard to cumulative doses in acceptable ranges (0.01 to 0.02 mg/kg) for buprenorphine HCl (0.3 mg/mL), which is commonly administered twice daily over 3 days to NHP.[13,15]

A secondary objective of this study was to evaluate the incidence of cutaneous injection site reactions associated with BupHClER formulation. The new BupBaseER formulation addresses concerns about skin reactions seen with BupHClER. Multiple acute cutaneous and subcutaneous reactions at the injection site have been reported after the use of Bup HCl ER in multiple species.[5,6,9,16,18,20,33,39,40] Further investigation revealed that these injection site reactions were most likely due to the selected solvent used to dissolve the active drug in the copolymer to form a homogeneous solution.[5,16,20] BupHClER combines buprenorphine hydrochloride with the original polymer matrix, which contains the solvent N-methyl-2-pyrrolidone that is stabilized by the addition of the antioxidant α-tocopherol to dissolve the active drug and form a solution.

In 2016, BupBaseER was developed with adjusted polymer ratios by using the buprenorphine base active pharmaceutical ingredient with the patented polymer and a different solvent, triacetin, to dissolve the active base in the polymer matrix and form a solution. We hypothesized that the BupBaseER formulation, which contains a modified polymer-based vehicle and solvent, would eliminate or reduce skin lesions at the injection site.

Materials and Methods

Animals. Five adult female cynomolgus macaques (*M. fascicularis*; age, 5.3 ± 0.1 y; weight, 3.8 ± 0.8 kg) and 13 adult male cynomolgus macaques (*M. fascicularis*; age, 6.7 ± 2.9 y; weight, 7.9 ± 1.1 kg) were used to complete this study. All animals were identified with a unique tattoo number. All procedures were conducted under an approved protocol from the Charles River NHP Import and Quarantine Sites IACUC (P-04122021).

Macaques were housed in accordance with the *Guide for the Care and Use of Laboratory Animals*,[23] Public Health Service Policy,[34] and Animal Welfare Act[3] and Regulations[4] in an AAALAC-accredited facility. Animals were pair-housed whenever possible and housed in visual and auditory contact with conspecifics; they received Purina 5045 Monkey Diet (25% crude protein, 5% crude fat, 6.5% crude fiber; Purina Mills, St Louis, MO) twice daily and municipal tap water ad libitum. Fresh produce or foraging materials were provided once daily. Rooms were maintained at 21 ± 2 °C and 30 to 70% relative humidity with 100% conditioned air at 15 to 20 changes hourly. Fluorescent lighting was provided on a 12:12-h light:dark cycle (lights on, 0500 to 1700). Animals were housed in squeeze-back cages with a removable divider. All macaques were provided with manipulable enrichment (balls, toys, Kongs) and with auditory enrichment via a TV during the day. All animals were tuberculosis-free as determined by semiannual skin testing. The macaques received a physical examination by the study veterinarian prior to selection for the study and were deemed fit. All animals were negative for SIV, STLV, SRV and B-virus.

Animals were divided into 2 groups that were balanced for age, sex, and weight. Group 1 (n = 6; 3 male and 3 female) was designated for the pharmacokinetic study, and group 2 (n = 12; 10 male and 2 female) were designated for skin reaction assessment. Only 2 females of the desired target age and weight range were available at the time of study.

Animal handling. During the pretreatment physical examination, all animals (groups 1 and 2) were sedated with ketamine (10 mg/kg), weighed, and the dorsoscapular areas were shaved for easy observation of the injection site. Animals designated for the pharmacokinetic study (group 1, n = 6) were fitted with an appropriate-sized primate collar (nylon; Primate Products, Miami, FL). All macaques in this group were handled without anesthesia for the duration of the study by using the pole-and-collar method.[2,32] By using positive reinforcement, all animals were habituated to being caught on the pole and transferred to a rolling chair-restraint device (Knowlton Machine, Ashland, OH). The collar was securely locked into a chair-restraint latch and the limbs could be manipulated, allowing blood collection. Animals were returned promptly to their home cage after blood collection. Food rewards were given during blood collection and when macaques were returned to their home caging. Macaques were allowed to resocialize immediately after each blood collection when a compatible partner was available.

Drugs. Group 1 macaques received single subcutaneous injections at 0.06 and 0.12 mg/kg of active BupBaseER (10 mg/mL; ZooPharm, Fort Collins, CO) with a minimum of 2 wk between doses. All macaques were weighed before each injection to ensure accurate drug dosing. The subcutaneous injection was administered in the scapular region of appropriately restrained animals by using a syringe of appropriate size with a 23-gauge, 1-in. needle. Drugs were administered in accordance with manufacturer's recommendations by tenting the skin and inserting the needle's full length under the skin. The drug was injected slowly over 10 to 15 s, and the needle was slowly withdrawn while the skin at the needle exit site was pinched for 5 to 10 s after needle withdrawal. Injections were done on alert animals that were restrained in chairs, as described above.

Group 2 macaques received 2 injections of each of 3 compounds—the original polymer matrix vehicle used in BupHClER; the modified polymer matrix vehicle used in BupBaseER; and 0.9% saline (Braun Medical, Bethlehem, PA)—on designated areas in the dorsoscapular region. All 3 injections were administered at the same time. Saline was used as a control at 0.02 mL/kg. The volumes of matrix copolymers and solvent administered for group 2 were equivalent to a calculated dosage of 0.2 mg/kg of a 10 mg/mL BupHClER or BupBaseER formulation. All macaques in group 2 were weighed before injections to ensure accurate dose calculation. Six specific areas in the dorsoscapular region were shaved, and all compounds

were administered during the pretreatment physical examination. Dose sites 1 and 2 (cranial aspect) were used for the control (saline 0.9%), sites 3 and 4 (mid dorsum) were used for the BupHClER polymer matrix formulation, and sites 5 and 6 (caudal aspect) were used for BupBaseER polymer matrix formulation. All compounds were administered in accordance with the manufacturer's recommendation, as mentioned above. Doses, sites, and times of administration were recorded.

Sample collection. For group 1, blood samples were collected at 10 time points for each round of dose administration. To determine whole-blood concentrations of buprenorphine, blood samples (1 mL each) were collected into EDTA tubes at each of 10 designated time points. An initial blood sample was collected just prior to administration (0 h) of a single dose of BupBaseER (0.06 mg/kg SC). Blood samples were then collected at 1, 4, 8, 12, 24, 48, 72, 96, and 120 h after dose administration. All time points were based on the dose administration. Animals were handled without anesthesia and had access to food and water throughout the study. After a 14-d washout period, the dosing and blood collection procedures were repeated by using BupBaseER (0.12 mg/kg SC). After each sample collection time point, blood tubes were placed in a rack and stored at –80 °C until shipment on dry ice for analysis (NorthEast BioLab, Hamden, CT).

Animal observations. The health of the macaques was monitored throughout the course of the study. All macaques underwent a complete physical exam at 10 d (group 1) or 24 h (group 2) prior to initiation of the study. Macaques were evaluated daily by cageside observation to monitor food consumption. For group 1, blood pressure, heart rate, respiratory rate, and body temperature were checked once daily during blood sample collection while the animals were in the restraint chair and once weekly during washout period.

In both groups, injection site reactions were monitored for 30 d after injection during cageside observations by using the method of modified Draize dermal scoring (Figure 1).[10] This system was used to assess presence of skin irritations including erythema, edema, and presence of scabbing.

Sample analysis. All blood samples were analyzed for buprenorphine concentrations (Northeast Bioanalytical Laboratories) by using liquid chromatography–tandem mass spectrometry. Published reports confirm the storage stability of frozen whole blood for buprenorphine at –20 °C as 119 d, benchtop stability as 20 h, and freeze–thaw stability through 3 cycles.[22] The blood:plasma distribution of buprenorphine ranges between 1.0 and 1.4, so the concentrations we expected from blood were similar to those we previously reported in plasma.[30] Samples were thawed on the bench top at room temperature, vortexed for at least 1 min, and aliquoted in volumes of 25 µL into 300-µL V-bottom polypropylene HPLC vials. Next, 25 µL of methanol was added, resulting in a 50:50 methanol:water solution. For calibration and quality controls, the diluent contained BupBaseER standard and blank prefrozen blood. Protein was precipitated by adding 150 µL acetonitrile containing 250 ng/mL of d4-buprenorphine as the internal standard. All tubes were then capped, vortexed for 3 min, and centrifuged for 3 min at 3,000 rpm (Allegra 6R centrifuge with GH 3.8 swinging bucket rotor, Beckman, Brea, CA). Analysis was performed on an Agilent 1200 HPLC system with a PE 200 autosampler (Perkin Elmer, Waltham, MA) and Triple-Quad API 5000 (Sciex, Framingham, MA). The column used was a Hypersil BDS column (50 × 2 mm C18-[5 µm], Phenomenex, Torrance, CA). The lower limit of quantitation of the assay was 0.25 ng/mL, and the upper limit of quantitation was 200 ng/mL.

Pharmacokinetics and statistical analysis Pharmacokinetic analysis was performed using whole-blood concentration and the time of blood collection after subcutaneous administration of BupBaseER to cynomolgus monkeys. Any quantifiable concentration data that were obtained after a nonquantifiable sample were treated as missing and not included in the analysis. Peak blood concentrations, the time of the peak blood concentration, and the time of the last observed quantifiable concentration were determined directly from the concentration–time data of each individual macaque. Pharmacokinetic parameters (AUC_{Tlast}, effective $t_{1/2}$; and mean residence time) were derived by using a model-independent approach (WinNonlin version 8.3, Certara USA, Princeton, NJ).[17] AUC_{Tlast} was determined by using the linear trapezoidal rule, and the effective $t_{1/2}$ was calculated by multiplying the mean residence time by the natural logarithm of 2. Elimination parameters were not determined due to the extended-release formulation. The time above the hypothesized therapeutic thresholds (0.1 ng/mL) were determined for each subject by subtracting the initial time at which buprenorphine concentrations exceeded the therapeutic thresholds of 0.1 or 0.5 ng/mL from the maximum time when buprenorphine concentrations were above the therapeutic threshold.[22] Descriptive statistics (n, mean, and SD) were determined and reported for the pharmacokinetic parameters.

		Score
Erythema	No erythema	0
	Very slight erythema, barely perceptible (edges of area not defined)	1
	Well-defined erythema, slight (pale red in color)	2
	Moderate to severe erythema (definite red in color)	3
	Severe erythema (beet or crimson red in color)	4
	Total possible erythema score	4
Edema	No edema	0
	Barely perceptible, very slight edema (edges of area not defined)	1
	Slight edema (edges of area not definable, but definite raising)	2
	Moderate edema (area well defined and raised approximately 1 mm)	3
	Severe edema (raised more than 1 mm)	4
	Total possible edema score	4
Eschar	No scab present	0
	Scab present	1
	Ulceration present	2
	Total possible eschar score	3

The absence or presence of findings was recorded for individual animals at the injection site observations.

Figure 1. Modified Draize injection site observations and dermal scoring scheme.

Results

Animal health. Throughout the study, all macaques remained healthy. All pairs remained socially housed throughout the study, with no adverse effect on social housing noted due to animal manipulation. Throughout the trials, macaques remained cooperative to handling. Blood pressure, heart rate, respiratory rate, and body temperature were stable throughout the study with no significant changes.

Tissue reaction at injection site. In both groups, injection sites were monitored daily for 30 d after injection. Only one cynomolgus macaque (in group 2) had a mild skin reaction (erythema and edema scores of 1) after receiving BupHClER. At 30 d after subcutaneous administration, none of the animals had any skin reactions to BupBaseER.

Pharmacokinetics. The blood buprenorphine concentrations after the administration of LDB and HDB (Figure 2) were assessed over a 120-h period. The blood buprenorphine concentration–time profiles were variable over the evaluation period for both doses (Figure 3) and both sexes. As a result, data from male and female macaques were combined at each dose due to the limited sample size. Mean blood buprenorphine concentrations were quantifiable for as long as 48 h after the administration of LDB and for as long as 120 h after HDB. The limit of detection of the assay was 0.25 ng/mL; any results that were below the limit of detection were reported as 0 by the lab and results were not included in the analysis. The hypothesis of interest was whether the buprenorphine concentration exceeded 0.1 ng/mL at the 48- and 120-h time points. Systemic exposure (peak blood concentration and AUC) of BupBaseER increased in a dose-proportional manner (Table 1). Maximum BupBaseER concentrations occurred at approximately 12 h after dosing (Table 1), and concentrations remained above 0.1 ng/mL for approximately 44 h for LDB and 103 h for HDB (Table 2). Furthermore, concentrations remained above the human therapeutic threshold (0.5 ng/mL) for approximately 30 h after LDB and 87 h after HDB (Table 2).

Discussion

Ensuring that animals receive sufficient analgesia for an appropriate length of time after an injury or surgical procedure can be challenging. Dosing frequency and timing are often centered around a standard workday and are somewhat empirically derived. This practice can result in periods during which animals have subtherapeutic levels of analgesic. Additional restraint frequently is required to repeatedly dose the animals. This result in stress, which has been shown to increase analgesia dose requirements in humans and could results in other complications.[28,29,42] Furthermore, NHP pose a challenge for drug administration because they must cooperate, be physically or chemical restrained, or require use of a remote delivery system for redosing. In addition, a lower frequency of restraint and dosing reduces the risk of human injury. In a research setting, administering injections to NHP requires gently bringing the animals to the front of the cage by squeezing. Repeated use of squeeze restraint for injections can be a significant stressor during the postoperative recovery period. Depending on the drug, some of these injections may fall during the dark or 'lights off' period in the NHP housing room, thus requiring turning on the lights, disrupting standard light cycles, and causing further stress.

Significant advantages are gained when a single injection of analgesic can provide 48 to 72 h of pain management as compared with the need for 6 to 9 injections to provide the same 48- to 72-h level of effective analgesia. The BupBaseER formulation offers an attractive way to overcome these obstacles. This extended-release formulation can be administered at the

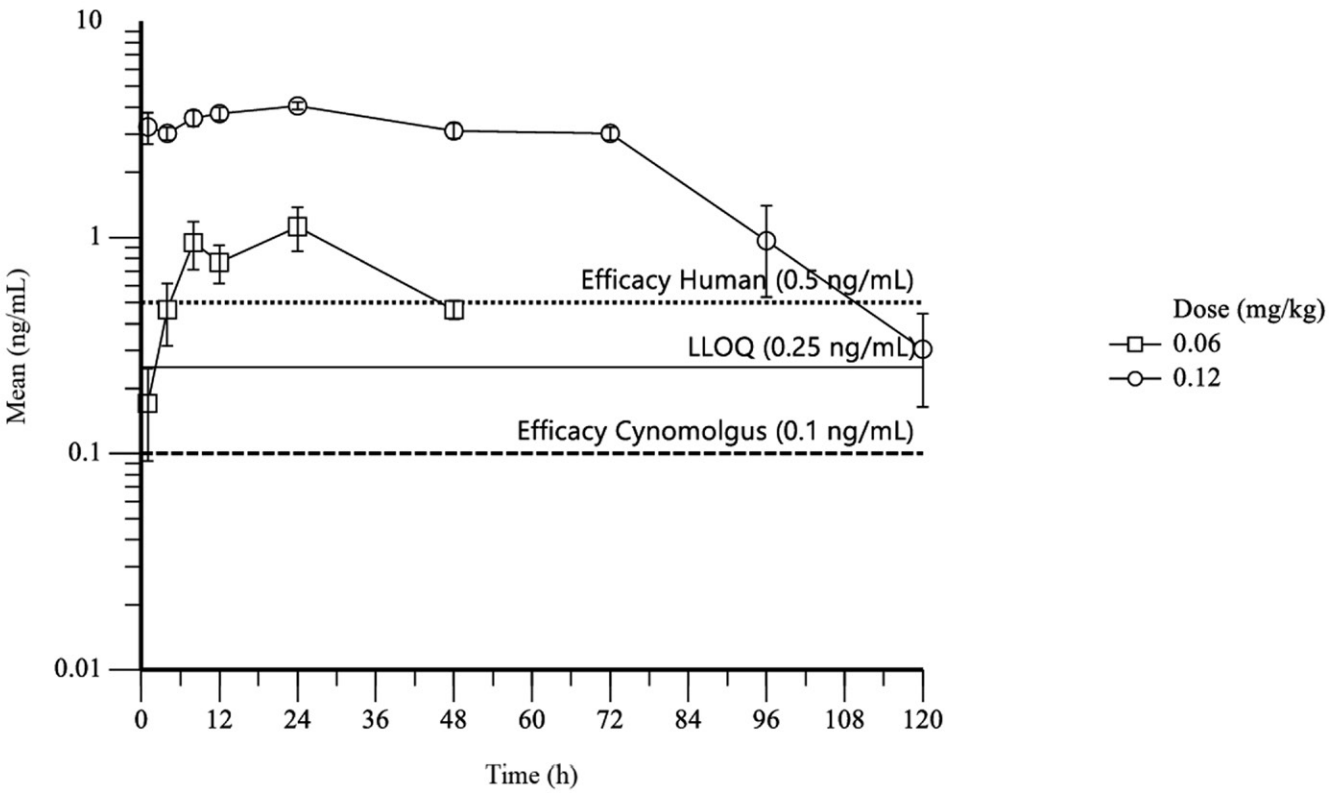

Figure 2. Buprenorphine whole-blood concentration–time profiles (mean ± 1 SD; n = 18) after a single subcutaneous injection of 0.06 or 0.12 mg/kg BupBaseER to male and female macaques. LLOQ, lower limit of quantification

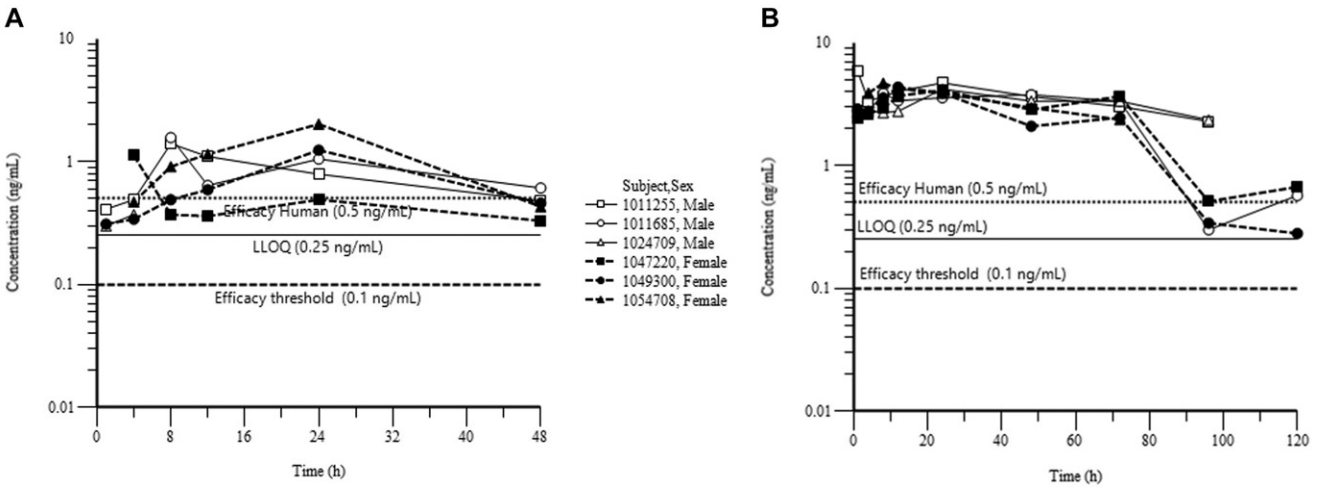

Figure 3. Buprenorphine whole-blood concentration–time profiles in individual male and female macaques after a single subcutaneous injection of (A) 0.06 mg/kg or (B) 0.12 mg/kg BupBaseER.

time of the procedure, eliminating concerns regarding timing, compliance, and necessary handling stressors for administration of additional doses.

This study evaluated the modified polymer matrix formulation of BupBaseER (10 mg/mL) in cynomolgus macaques (*M. fascicularis*). We determined whether 2 dosage levels—0.06 and 0.12 mg/kg—would reach and maintain blood levels above 0.1 ng/mL level for 24 and 48 h, respectively. Our data showed that LDB (0.06 mg/kg) and HDB (0.12 mg/kg) maintained concentration levels 3 times higher than the hypothesized putative therapeutic threshold of 0.1 ng/mL for approximately 44 h and 103 h, respectively (Figure 3). These results indicate that buprenorphine concentrations likely remained well above the therapeutic threshold beyond the span of this study. Additional studies are needed to determine the frequency of administration needed to maintain therapeutic buprenorphine concentrations for longer periods of time.

Table 1. Whole-blood pharmacokinetic parameters (mean ± 1 SD; n = 6) after a single subcutaneous injection of BupBaseER to male and female macaques as a group

	Dose (mg/kg) of BupBaseER	
	0.06	0.12[a]
C_{max} (ng/mL)	1.29 ± 0.548[a]	4.52 ± 0.746
T_{max} (h)	12 ± 9.47[a]	12.8 ± 9.35
T_{last} (h)	40.7 ± 18.0	104 ± 19.6
AUC_{Tlast} (ng × h/mL)	37.6 ± 12.4[b]	294 ± 38.3
MRT (h)	22.8 ± 1.43[b]	41.9 ± 5.4
Eff $t_{1/2}$ (h)	15.8 ± 1.0[b]	29.0 ± 3.7

C_{max}, peak blood concentration; Eff $t_{1/2}$, effective half-life; MRT, mean residence time; T_{last}, time at last measurable concentration; T_{max}, time at C_{max}
[a]Number of animals: n = 6.
[b]Number of animals: n = 5.

Table 2. Duration of buprenorphine concentrations above therapeutic threshold concentration after a single subcutaneous injection of BupBaseER to male and female macaques as a group (n = 6)

	Dose (mg/kg) of BupBaseER	
Threshold (ng/mL)	0.06	0.12
0.1	44.4 ± 17.1	103 ± 19.6
0.5	29.6 ± 19.5[a]	87.0 ± 19.6

Mean time (h) ± SD above threshold.
[a]Number of animals: n = 5.

Buprenorphine concentration data indicated that individual concentrations exceeded the targeted 0.1 ng/mL threshold at 3.2 h and 1 h on average after injection of LDB (0.06 mg/kg) and HDB (0.12 mg/kg, respectively). This finding suggests that administrating pain medication prior to or during a procedure, as well as the use of multimodal analgesia regimen, ensures that therapeutic levels are present at the end of the procedure, thus minimizing the gap between effective analgesia and recovery from anesthesia.

A limitation of this study was that the lower limit of quantitation for the BupBaseER assay (0.25 ng/mL) was higher than the therapeutic threshold of 0.1 ng/mL. This assay limitation may have impacted the observed duration of time buprenorphine was above the therapeutic threshold for animals administered BupBaseER at a low dose, 0.06 mg/kg, after 48 h time point. This also affected the interpretation of the time it takes to reach therapeutic concentrations. As stated above, the desirable 0.1 ng/mL threshold was exceeded by 3.2 h on average following injection of LDB (0.06 mg/kg); however, this is a conservative measurement as the average threshold may have been achieved sooner. Although not necessarily a limitation, we used whole blood rather than plasma for measurement of buprenorphine concentration due to the size of the animals, the total amount of blood that can safely be collected, and the required amount of plasma needed. As compared with plasma, whole blood requires more careful collection and handling during sample processing.

Because various adverse effects have been reported in animals given BupHClER, a secondary objective of this study was to compare the incidence of injection site reactions between the BupHClER and BupBaseER formulations. Past reports have included tissue reactions like erythema, raised pink plaques, scabbing, and sterile abscesses at the injection site.[6,9,33,39,40]

A variety of biocompatible solvents at various ratios have been used with the biodegradable 1 liquid DL-lactide-cocaprolactone copolymer carrier matrix in order to generate a slow release of buprenorphine after subcutaneous administration. BupBaseER was formulated with adjusted polymer ratios that added a small amount of N-methyl-2-pyrrolidone as a solvent to dissolve the active pharmaceutical ingredient and also included triacetin solvent so that all ingredients could be

combined into a homogeneous, copolymer and drug solution. This modified BupBaseER solution has been associated with fewer or no injection site reactions in NHP, in contrast to previous reports with the BupHClER formulation.

Although the novel BupBaseER formulation reduced the injection-related reactions previously reported, adverse events may still occur under some circumstances. For example, a previous report described small cutaneous lesions at point of injection and small, fibrous lumps that begin to appear as long as 1 to 2 wk after injection.[18] These bumps are purported to occur due to an injection that at some point either contacted or penetrated muscle, leading to disruption of the microvascular bed and the formation of necrotic tissue at the site. All ER formulations were designed for subcutaneous administration, allowing the polymer to precipitate and coagulate upon contact with aqueous body fluid, thus forming a gelatinous implant matrix. This process requires that the drug be injected subcutaneously into the loose skin to adequately accommodate the implant in an unencumbered subcutaneous space.

To avoid any leakage of polymer contents from the injection site, the manufacturer recommends that the injection should be given by tenting the skin and using an appropriately sized needle on a dosing syringe. A new needle should replace the needle that was used to draw the drug from the bottle, thus preventing introduction of the previous product in the needle into the skin. The needle's full length should be inserted under the skin, the formulation should be injected slowly over 10 to 15 s, and the needle slowly withdrawn. Finally the skin at the needle exit site should be pinched upon needle withdrawal and remain pinched for 5 to 10 s afterward.

In conclusion, these results showed that buprenorphine concentrations likely remain well above the therapeutic threshold beyond the span of this study. These findings suggest a new dosing strategy and adjustment to dosing and frequency to the extended-release buprenorphine given to NHPs. BupBaseER is a valuable medication for pain management in NHP that can reduce animal stress, improve animal welfare, and simplify the management of postoperative analgesia within research and zoological settings.

Acknowledgments

To remain compliant with the most current regulatory guidelines, Zoopharm updated the labeling on SR formulations to ER. The label change took effect on July 1, 2022.

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