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A Phase I Study of the Pharmacokinetics, Pharmacodynamics, and Safety of Liposomal Bupivacaine for Sciatic Nerve Block in the Popliteal Fossa for Bunionectomy

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Abstract

This trial assessed the pharmacokinetics, pharmacodynamics, and safety of liposomal bupivacaine given via ultrasound-guided popliteal sciatic nerve block with or without immediate-release bupivacaine hydrochloride in adults having bunionectomies. Forty-five adults were enrolled into four sequential cohorts: (1) liposomal bupivacaine 266 mg with bupivacaine hydrochloride 50 mg; (2) liposomal bupivacaine 133 mg with bupivacaine hydrochloride 50 mg; (3) liposomal bupivacaine 266 mg; or (4) bupivacaine hydrochloride 100 mg. Outcomes included pharmacokinetics (e.g., bupivacaine maximum plasma concentration [C_{max}]), onset and duration of motor and sensory nerve block, and safety. Liposomal bupivacaine admixed with bupivacaine hydrochloride produced biphasic bupivacaine plasma disposition profiles with two distinct peaks. Geometric mean C_{max} of the early peak ranged from 235 to 421 ng/mL and the geometric mean of the late C_{max} was ~30%-50% lower than the early peak. Median time to sensory block onset was 18 to 29 min in all cohorts. Sensory blocks lasted about twice as long with liposomal bupivacaine (median, 119-167 h) than with bupivacaine hydrochloride alone (median, 67 h). There were no serious adverse events. In conclusion, liposomal bupivacaine provided prolonged sensory nerve block when given as popliteal sciatic nerve blocks with or without bupivacaine hydrochloride, and bupivacaine plasma concentrations were well below the lower bound of the toxicity threshold of 2000 ng/mL for all cohorts.

Keywords

anesthesia, foot and ankle surgery, immediate-release bupivacaine, liposomes, postoperative pain, ultrasound-guided nerve block

Introduction

Foot and ankle surgery typically produce substantial postoperative pain.[1] Inadequate postoperative analgesia promotes use of rescue opioids, increases hospital costs, delays hospital discharge, increases hospital readmissions, and reduces quality of life.[2] Guidelines for foot and ankle surgery recommend using multimodal approaches that include therapies with differing mechanisms of action, such as nonsteroidal anti-inflammatory drugs, regional anesthesia, and opioids.[3] Sciatic nerve blocks in the popliteal fossa (popliteal sciatic nerve blocks) provide analgesia for foot and

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ankle procedures and improve patient recovery.[4] Furthermore, analgesia from sciatic nerve blocks generally lasts longer than that from more distal blocks.[4,5]

Delivery of local anesthetics over a prolonged period with infusion pumps and catheters can provide prolonged analgesia.[6,7] However, continuous local anesthetic infusion can cause complications including drug leakage and catheter dislodgement or blockage.[6] A potential alternative for prolonged analgesia using catheters is liposomal bupivacaine, a long-acting formulation of bupivacaine that was most recently approved by the US Food and Drug Administration for postsurgical local analgesia in adults via a sciatic nerve block in the popliteal fossa and via adductor canal block.[8] Liposomal bupivacaine is designed to release low doses of bupivacaine over several days, providing prolonged analgesia while avoiding high plasma concentrations of local anesthetics that can cause cardiac and neurologic complications.[9–14] In a phase 3 trial of participants who received liposomal bupivacaine or bupivacaine hydrochloride (HCl) as a popliteal sciatic nerve block for bunionectomy, Schwartz and colleagues reported that liposomal bupivacaine provided analgesia over 4 days after surgery, which was substantially longer than with bupivacaine HCl.[15] However, the pharmacokinetics, pharmacodynamics, and safety of liposomal bupivacaine have not been characterized when admixed with bupivacaine HCl for popliteal sciatic nerve blocks. The objective of this trial was therefore to assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of liposomal bupivacaine alone and admixed with bupivacaine HCl for popliteal sciatic nerve blocks in patients having bunionectomies.

Methods

This phase 1, single-center, open-label, dose-escalation trial was approved by the Western Institutional Review Board (Puyallup, WA; protocol #20191731) on July 3, 2019, and was registered at ClinicalTrials.gov (NCT04002089) before the first participant was enrolled. Written informed consent was obtained from each participant, and trial conduct was consistent with the current International Council for Harmonisation Good Clinical Practice (E6) and Declaration of Helsinki guidelines. The trial was conducted from July 26, 2019 to December 2, 2019, at First Surgical Hospital (Bellaire, TX).

Participant Eligibility

Adults scheduled for bunionectomy procedures who were designated American Society of Anesthesiologists (ASA) physical status classification I-III and had a body mass index (BMI) $\geq$18 and $\leq$40 kg/m^2 were eligible. Exclusion criteria included inadequate sensory function on the operative foot, concurrent physical conditions that might require analgesic treatment in the postdosing period for pain, history of diabetes or severe peripheral vascular disease, renal or hepatic dysfunction, and long-term opioid use (defined as $\geq$30 morphine equivalents per day in the last 30 days).

Dose Selection, Procedures, and Treatment Cohorts

Dose Selection and Study Cohorts. Prior pharmacokinetic research demonstrated that administration of liposomal bupivacaine 266 mg resulted in a maximum plasma concentration of bupivacaine equivalent to that produced by administration of standard bupivacaine HCl 100 mg.[9] Additionally, previous work showed that both liposomal bupivacaine 133 mg and liposomal bupivacaine 266 mg were safe for administration,[15] and these two doses reflect the approved doses for nerve blocks and local infiltration, respectively, in the label for liposomal bupivacaine.[8] Moreover, given bupivacaine HCl may be admixed with liposomal bupivacaine to provide early analgesic coverage as bupivacaine is gradually released from liposomal bupivacaine, cohorts with admixed liposomal bupivacaine and bupivacaine were planned to fully characterize the safety and pharmacokinetics over a broad range of cumulative bupivacaine doses.

Based on the dose selection considerations above, participants were enrolled into four cohorts, which were enrolled sequentially. Because the study was open label, investigators, study personnel, and participants were not blinded to treatment assignment. The first cohort was given liposomal bupivacaine 266 mg admixed with immediate-release bupivacaine HCl 50 mg in a total volume of 30 mL (liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg cohort), cohort 2 was given liposomal bupivacaine 133 mg admixed with bupivacaine HCl 50 mg in a total volume of 20 mL (liposomal bupivacaine 133 mg + bupivacaine HCl 50 mg cohort), and cohort 3 was given liposomal bupivacaine 266 mg in 20 mL volume (liposomal bupivacaine 266 mg cohort). The fourth cohort was given bupivacaine HCl 100 mg in a volume of 20 mL (bupivacaine HCl 100 mg cohort).

Procedure and Pain Management. Participants were not permitted to receive systemic glucocorticoids or neuroleptic drugs, long-acting opioids, nonsteroidal anti-inflammatory drugs, dexmedetomidine, or opioids before administration of the sciatic nerve block. Local anesthetics were administered via ultrasound-guided popliteal sciatic nerve block 60 ($\pm$30) min before bunionectomies. Ultrasound video was captured for all participants and was used to confirm proper block administration.

Liposomal bupivacaine was not admixed with other drugs (e.g., epinephrine, dexamethasone, or clonidine), nor were other local anesthetics, such as lidocaine, permitted. Drug preparation and administration were reviewed by the field clinical trial liaisons during the study initiation visits; field clinical trial liaisons also observed the first study drug administration at the trial site to confirm the block was administered appropriately. The bunionectomies were performed with general anesthesia or propofol sedation at the discretion of the clinician. Only short-acting opioids, such as fentanyl, sufentanil, or remifentanil, were permitted during surgery; ketamine and midazolam were not used.

Postsurgical pain intensity was scored on an 11-point numerical rating scale, where 0 = no pain and 10 = worst imaginable pain. Pain intensity was assessed once daily on postoperative days 1 through 5 (within 6 h of noon) and at discharge. Participants with pain score <5 were given nonsteroidal anti-inflammatory drugs, and participants with pain score ≥5 were given immediate-release oxycodone or intravenous morphine or hydromorphone if oral medication was not tolerable or if oxycodone rescue failed. No other analgesics were permitted within 96 h after the sciatic nerve blocks.

Endpoints and Assessments

Pharmacokinetics Measurements. Blood samples for pharmacokinetic assessments were obtained at baseline and at 0.5, 0.75, 1, 2, 12, 24, 60, 72, 84, 96, 120, 144, and 168 h after sciatic nerve blocks, and plasma samples were shipped on dry ice for analysis (ABS Laboratories, York, UK). Determination of bupivacaine plasma concentrations was performed as previously described.[15] Briefly, plasma samples were stored at −20°C until analysis; 50-µL samples containing analyte and internal standard (bupivacaine-d_9) were extracted using a liquid–liquid extraction procedure and analyzed using high-performance liquid chromatography tandem mass spectrometry (AB/MDS Sciex 4000 mass spectrometer); positive ions were monitored in the multiple reaction monitoring mode.

Analyte concentration was determined using Applied Biosystems analyst 1.6.1 with a weighted least squares ($1/x^2$) linear regression on the peak area ratios from calibration standards. The lower limit of quantitation was 1 ng/mL, and the upper limit of quantitation was 1000 ng/mL. Pharmacokinetics endpoints included area under the plasma concentration versus time curve (AUC), maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), apparent terminal elimination half-life, apparent clearance, and apparent volume of distribution. Early C_{max} was defined as C_{max} observed between dosing (0 elapsed hours) and 2 h after dose, and late C_{max} was defined as C_{max} >2 h after dosing. Early T_{max} is the time of early $C_{max,}$ and late T_{max} is the time of late C_{max}.

Noncompartmental Analysis. For statistical analysis, the pharmacokinetics population included all participants who received study drugs and provided sufficient samples for calculation of pharmacokinetic parameter estimation. Observed mean pharmacokinetic concentrations and pharmacokinetic variables, derived from noncompartmental analysis, are reported.[16] Pharmacokinetic variables were generated using Phoenix WinNonlin, version 8.2 (Certara, USA, Inc.) software. Actual sampling time relative to drug administration was used for all calculations of pharmacokinetic variables, and missing concentration data were not imputed. Pharmacokinetic parameters were summarized by cohort using descriptive statistics. Adjusted R^2 values ≥0.85 were considered acceptable for apparent terminal elimination rate constant estimation.

Population Pharmacokinetic Modeling. A nonlinear mixed-effects modeling approach was used to build a population pharmacokinetics model that describes the bupivacaine plasma concentration–time course and liposome release kinetics. Model development was carried out using the first-order conditional estimation with interaction. Generally, models were developed in order of increasing complexity and proceeding until further improvement in fit was not supported by the data. This principle was applied to the search for structural model components (absorption model structure or the number of apparent distribution compartments) as well as the random effects (interindividual variability and residual unexplained variability). During model development, a difference in objective function value (ΔOFV) of 3.84 was used between two nested models differing in one parameter (corresponding to a nominal $P < .05$). The final model was determined based on maximized likelihood (lowest stable OFV), physiological plausibility of parameter values, successful numerical convergence, parameter precision, and acceptable visual predictive check using 1000 simulations.[17] A formal covariate analysis was not conducted since the random effects of the pharmacokinetic model captured the influence of intrinsic and extrinsic factors on liposomal bupivacaine pharmacokinetics, leaving the exposure-response analysis unaffected.

Pharmacodynamics Measurements. Pharmacodynamics endpoints included average time to onset and average duration of motor and sensory block. Onset was assessed 15, 30, and 45 min after injection, and duration

was assessed at 1, 2, 12, 24, 60, 72, 84, 96, 120, 144, and 168 h after the blocks. The time to onset and duration of sensory block were assessed by response to pinprick tests. Onset of sensory block was defined by loss of sensation to pinprick along the distribution of the sciatic nerve block below the level of the block compared with the contralateral leg. Sensory block duration was defined as the time from onset to complete recovery of sensation on two consecutive evaluations. Onset of motor block was defined as the earliest time with some impairment of plantar/dorsiflexion of the ankle, and duration was defined as the time to return of complete foot movement. For statistical analysis, time to onset of motor block and sensory block were summarized by median and quartiles estimated using the Kaplan–Meier method and reported using descriptive statistics.

Exposure-Response Analysis. Motor and sensory block responses were modeled using a nonlinear mixed-effects logistic regression model to characterize the exposure-response profile of each endpoint. Post hoc pharmacokinetic parameters from the pharmacokinetic model were used to generate individual predicted plasma concentrations to drive the response. Investigated exposure-response models included linear, maximum effect (E_{max}), and sigmoidal E_{max} models. The model selection criteria were similar to those described in the Population Pharmacokinetic Analysis subsection.

Safety Assessments and Exploratory Efficacy Assessments. Adverse events, including serious adverse events, were evaluated from the start of the block procedure through postoperative day 14. Pain intensity scores were collected on an 11-point numerical rating scale at discharge and daily from postoperative days 1 to 5, using the following questions: "what was your worst pain in the last 24 hours" and "what was your average pain in the last 24 hours?" Unscheduled numerical rating scale scores were obtained before rescue medications were given. The exploratory efficacy endpoint was AUC of the numerical rating scale pain intensity scores from 24 to 96 h after the procedure.

Statistical analysis of safety data included all participants who received study drugs.

Statistical Analysis

No formal sample size calculation was performed, but the planned 10 participants per cohort were deemed likely to provide a meaningful description of pharmacokinetics and pharmacodynamics. Exploratory efficacy endpoints were assessed in the safety population. Demographic and morphometric characteristics were summarized using descriptive statistics.

All nonlinear mixed-effects modeling analyses (including the exposure-response model) were carried out using NONMEM (Version 7.4, ICON Development Solutions).

Results

Participant Disposition

Forty-five participants were enrolled and completed the study (Figure 1). As planned, 10 participants were enrolled per cohort; an additional 5 participants were enrolled in the liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg cohort to replace 5 participants with insufficient pharmacokinetics data. All 45 participants were included in the safety analysis; 5 participants in the liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg cohort and 1 participant in the liposomal bupivacaine 133 mg + bupivacaine HCl 50 mg cohort were excluded from the pharmacokinetic analysis (n = 39) because of incomplete data.

Baseline Characteristics and Intraoperative Medications

Across enrolled participants, most were female (80%), white (71%), and designated ASA physical status classification I (67%; Table 1). All participants across cohorts received propofol except one participant in cohort 4. The proportion of participants who received sevoflurane varied by cohort, with 60% in cohort 1, 80% in cohort 2, 90% in cohort 3, and 10% in cohort 4.

Pharmacokinetics

The observed mean bupivacaine plasma concentration over time following population pharmacokinetic modeling is shown for all treatment cohorts in the safety analysis set (Figure 2). Bupivacaine pharmacokinetics from the noncompartmental analysis are summarized in Table 2. One participant given liposomal bupivacaine 266 mg alone and two participants given bupivacaine HCl 100 mg had adjusted R^2 values lower than 0.85 (the a priori acceptance level). Consequently, parameter estimates dependent on the estimated apparent terminal elimination rate ($AUC_{0-\infty}$, apparent terminal elimination half-life, apparent clearance, and apparent volume of distribution) were not included in the pharmacokinetic analyses. Plasma bupivacaine concentrations appeared to be dose proportional based on dose-normalized AUC. Median T_{max} values for the liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg cohort, liposomal bupivacaine 133 mg + bupivacaine HCl 50 mg cohort, and the liposomal bupivacaine 266 mg cohort, respectively, were consistent with prolonged exposure to bupivacaine after liposomal bupivacaine administration.

Population Pharmacokinetic Analysis

A total of 456 pharmacokinetic observations from 40 subjects were used for pharmacokinetic model

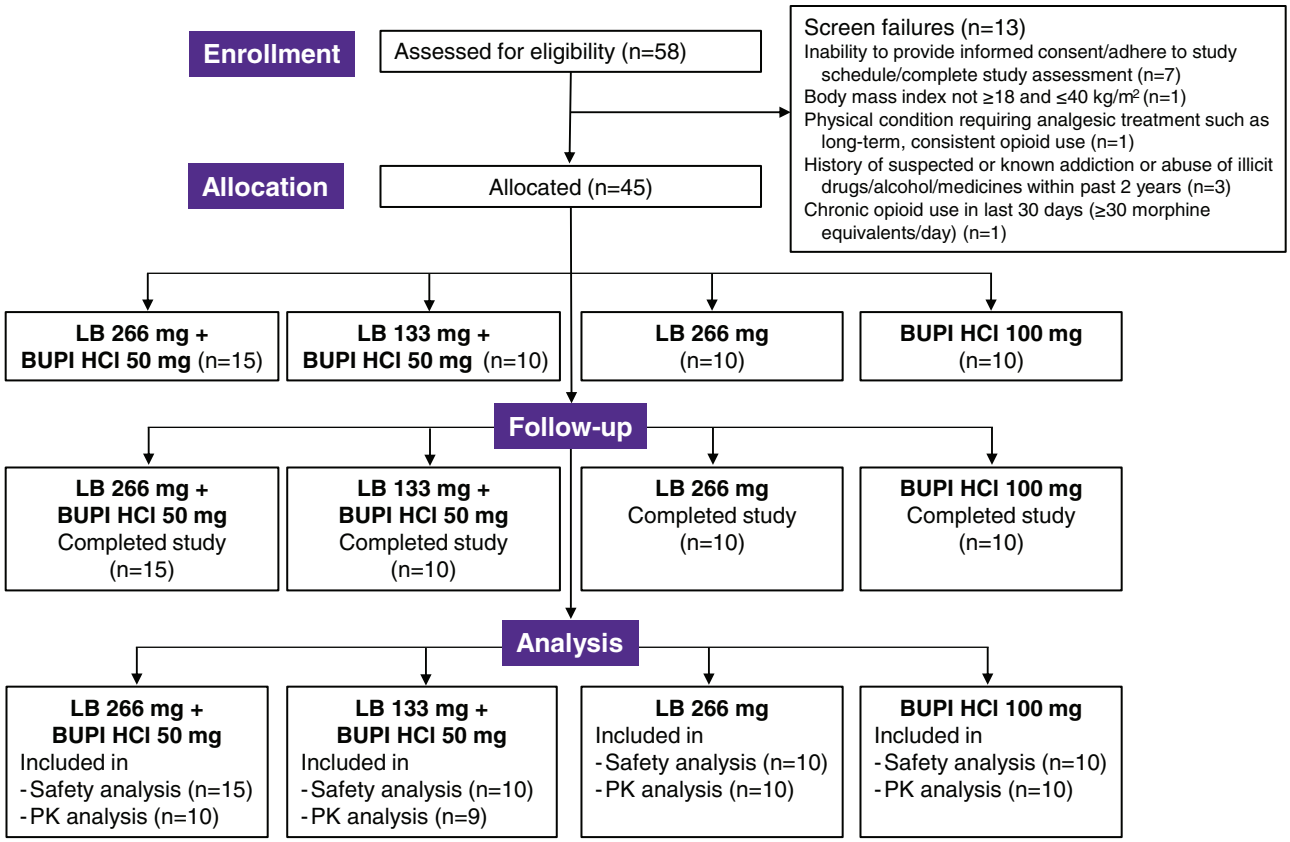

Figure 1. Participant disposition. BUPI HCl, bupivacaine hydrochloride; LB, liposomal bupivacaine; PK, pharmacokinetics.

Table 1. Baseline Participant Demographics and Characteristics

	LB 266 mg + BUPI HCl 50 mg (n = 15)	LB 133 mg + BUPI HCl 50 mg (n = 10)	LB 266 mg (n = 10)	BUPI HCl 100 mg (n = 10)
Age, mean (SD), y	48 (11)	48 (13)	51 (12)	48 (14)
Female, n (%)	14 (93)	8 (80)	8 (80)	6 (60)
Race, n (%)				
Asian	1 (7)	2 (20)	0 (0)	1 (10)
Black/African American	2 (13)	2 (20)	3 (30)	2 (20)
White	12 (80)	6 (60)	7 (70)	7 (70)
ASA physical status classification, n (%)				
I	13 (87)	4 (40)	4 (40)	9 (90)
II	2 (13)	6 (60)	6 (60)	1 (10)
BMI, mean (SD), kg/m^2	29 (4)	29 (5)	30 (6)	28 (4)

ASA, American Society of Anesthesiologists; BMI, body mass index; BUPI HCl, bupivacaine hydrochloride; LB, liposomal bupivacaine; SD, standard deviation.

building. Data from the five participants with incomplete pharmacokinetic data in the liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg cohort were excluded. The initial pharmacokinetic model comprised a simple, single-compartment disposition model with first-order elimination from the plasma compartment. Absorption of liposomal bupivacaine was described using a liposome dissolution compartment that slowly releases free bupivacaine, which is then rapidly absorbed into the systemic circulation. The immediate-release bupivacaine HCl solution followed the same rapid absorption process. To account for the immediate release of bupivacaine from its liposomal formulation after administration, liposomal bupivacaine burst and retention fractions (F_{ret}) were included. All absorption processes were characterized using first-order kinetics. Liposome dissolution was determined using a Weibull-type kinetics improved model fit ($\Delta OFV = -162.65$). Inclusion of a peripheral distribution compartment further improved the model fit ($\Delta OFV = -32.82$). One subject from the bupivacaine HCl 100 mg cohort was excluded owing to an inconsistent bupivacaine

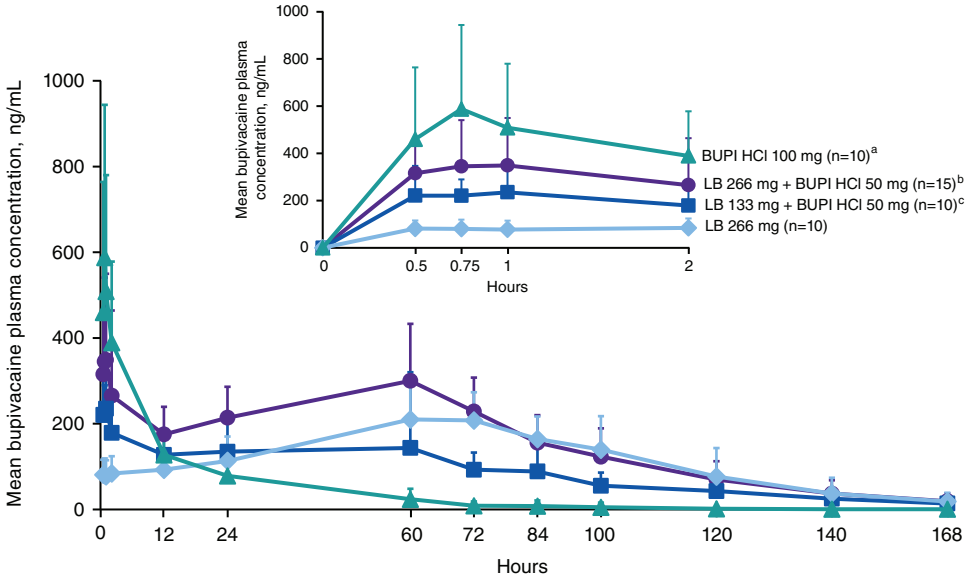

Figure 2. Observed mean plasma bupivacaine concentration profiles—population pharmacokinetic modeling. Error bars are the standard deviation. Inset shows mean plasma concentration from 0 to 2 h. [a]n = 9 at 72 and 96 h. [b]n = 14 at 0, 0.5, and 96 h; n = 12 at 12 and 84 h; n = 11 at 24 h; and n = 10 at 60 and 72 h. [c]n = 9 at 0.75, 1, 72, and 96 h; n = 8 at 144 and 168 h; and n = 7 at 24 h. BUPI HCl, bupivacaine hydrochloride; LB, liposomal bupivacaine.

concentration–time profile. Lastly, the bupivacaine absorption rate constant was fixed to a value from the bupivacaine HCl 100 mg cohort data to stabilize the pharmacokinetic model. Interindividual variability was included in the mean dissolution time (MDT), apparent clearance (CL/F), apparent central volume of distribution (V_c/F), and F_{ret}. Residual unexplained variability was modeled using a proportional error.

The final pharmacokinetic model was mathematically described as follows (mathematical model):

$$\frac{dLB}{dt} = -k_d \times LB$$

$$\frac{dFB}{dt} = k_d \times LB - k_a \times FB$$

$$\frac{dB}{dt} = -k_a \times B$$

$$\frac{dC}{dt} = k_a \times (B + FB) - (k_{cp} + k_{el}) \times C + k_{pc} \times P$$

$$\frac{dP}{dt} = k_{cp} \times C - k_{pc} \times P$$

$$k_{el} = \frac{CL}{V_c}; k_{cp} = \frac{Q}{V_c}; k_{pc} = \frac{Q}{V_p}; k_d = \frac{B}{MDT} \times \left(\frac{time}{MDT}\right)^{B-1}$$

where LB is the amount of administered liposomal bupivacaine, FB is the amount of free bupivacaine following dissolution or initial burst of the liposomal bupivacaine formulation, B is the administered amount of bupivacaine HCl in solution, and C and P are the amounts in the central and peripheral compartments. k_d is the dissolution rate described by a Weibull-like process composed of the MDT, and a shape factor, B. k_a refers to the absorption rate constant of free bupivacaine, k_{el} is the elimination rate constant, and k_{cp} and k_{pc} are the transfer rate constants between the central and peripheral compartments. CL and Q denote apparent clearance and apparent intercompartmental clearance, and V_c and V_p are the apparent central and apparent peripheral volumes of distribution, respectively.

The pharmacokinetics parameter estimates of the final pharmacokinetic model are displayed in Table S1. Following administration of the bupivacaine solution, free bupivacaine was rapidly absorbed and exhibited a biphasic disposition in plasma. After the administration of liposomal bupivacaine, the MDT was 58.1 h, with approximately 7% of the administered dose released immediately. The final pharmacokinetic model demonstrated appropriate agreement between predicted and observed bupivacaine concentrations (Figure S1). The conditional weighted residuals were randomly scattered around the predicted concentrations and across time, with no substantial deviation from the mean zero (Figure S2). Moreover, visual predictive checks demonstrated reasonable predictive performance of the final pharmacokinetic model, indicating no substantial model misspecifications (Figure S3).

Pharmacodynamics

Median time to sensory block onset ranged from 0.3 to 0.5 h and was comparable across all treatment cohorts (Figure 3). In contrast, the median duration of sensory block was ~80%-150% longer in the cohorts

Table 2. Bupivacaine Pharmacokinetic Parameter Estimates by Cohort—Noncompartmental Analysis

	LB 266 mg + BUPI HCl 50 mg (n = 10)	LB 133 mg + BUPI HCl 50 mg (n = 9)	LB 266 mg (n = 10)	BUPI HCl 100 mg (n = 10)
Dose normalized to bupivacaine free base, mg	310	177	266	89
$AUC_{0\text{-last}}$, n	10	9	10	10
Mean (SD), ng × h/mL	25,500 (6711)	11,500 (3404)	19,100 (6351)	6320 (1957)
Geometric mean (%CV)	24,700 (26)	11,000 (30)	18,300 (33)	6050 (31)
$AUC_{0\text{-}\infty}$, n	10	9	9	8
Mean (SD), ng × h/mL	26,500 (6896)	12,400 (4127)	20,600 (6469)	6700 (2066)
Geometric mean (%CV)	25,600 (26)	11,800 (33)	19,800 (31)	6400 (31)
Early C_{max}, n	10	9	10	10
Mean (SD), ng/mL	451 (196)	255 (113)	105 (38)	617 (366)
Geometric mean (%CV), ng/mL	421 (44)	235 (44)	97 (36)	496 (59)
Late C_{max}, n	10	9	10	NA
Mean (SD), ng/mL	313 (130)	127 (28)	239 (81)	
Geometric mean (%CV), ng/mL	291 (42)	123 (22)	226 (34)	
Early T_{max}, n	10	9	10	10
Median (range), h	0.6 (0.4-1.9)	0.7 (0.4-2.4)	1.0 (0.4-2.5)	0.8 (0.5-2.0)
Late T_{max}, n	10	9	10	NA
Median (range), h	59 (24-72)	24 (12-71)	65 (24-98)	
$t_{1/2}$, n	10	9	9	8
Mean (SD), h	23.0 (11.3)	33.1 (19.4)	18.8 (8.2)	10.4 (2.2)
Vd/F, n	10	9	9	8
Mean (SD), L	411 (212)	685 (309)	374 (191)	225 (110)
Geometric mean (%CV), L	359 (52)	630 (45)	337 (51)	206 (49)
CL/F, n	10	9	9	8
Mean (SD), L/h	12.6 (3.8)	15.9 (5.6)	14.0 (4.2)	14.6 (5.1)
Geometric mean (%CV), L/h	12.1 (30.2)	15.0 (35.4)	13.5 (29.7)	13.9 (34.9)

%CV, percent coefficient of variance; $AUC_{0\text{-}\infty}$, area under the plasma concentration versus time curve from time of dosing (0 h) to infinity; $AUC_{0\text{-last}}$, AUC from time of dosing (0 h) to the time of the last quantifiable concentration; BUPI HCl, bupivacaine hydrochloride; CL/F, apparent clearance; C_{max}, maximum plasma concentration; early C_{max}, C_{max} occurring between dosing (0 h) and 2 h after dosing; early T_{max}, time of early C_{max}; late C_{max}, C_{max} occurring >2 h after dosing; late T_{max}, time of late C_{max}; LB, liposomal bupivacaine; NA, not applicable; SD, standard deviation; $t_{1/2}$, apparent terminal elimination half-life; Vd/F, apparent volume of distribution.

receiving liposomal bupivacaine compared with the cohort receiving bupivacaine HCl 100 mg. Median duration of sensory block varied between 119 and 167 h for cohorts receiving liposomal bupivacaine compared with 67 h for the cohort receiving bupivacaine HCl alone. Some participants had not regained full normal sensation at 168 h after dosing (one participant in the liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg cohort and two participants in the liposomal bupivacaine 266 mg cohort); however, sensory block was fully resolved in these participants by the 14-day follow-up.

Exposure-Response Analysis

A total of 563 motor block data points and 556 sensory block data points from 39 subjects were used for exposure-response model development. The two endpoint models were developed separately. The starting model was a baseline motor block model. Incorporating linear (ΔOFV = −100.97), E_{max} (ΔOFV = −223.89), and sigmoidal E_{max} (ΔOFV = −236.93) drug effect models substantially improved the data fit. The latter model was selected for further development. The E_{max} parameter was fixed at 1 due to the constraint of the parameter space (probability cannot exceed 1). To account for potential delays between bupivacaine concentrations and response, an effect compartment model was explored, confirming the presence of a delay in motor response (ΔOFV = −32.61). Random effects were included on the half-maximum effect compartment concentration (EC_{50}) and the effect compartment equilibrium rate constant, k_{eq}. The sensory block model followed a similar development approach, resulting in the same exposure-response model. The parameter estimates of the motor and sensory block exposure-response model are displayed in Tables S2 and S3. Considering the relatively small sample, the motor and sensory block models reasonably captured the observed data (Figures S4 and S5).

Median time to onset of motor block was comparable between all treatment cohorts (Table 3). The median duration of motor block was 85%-143% longer in the

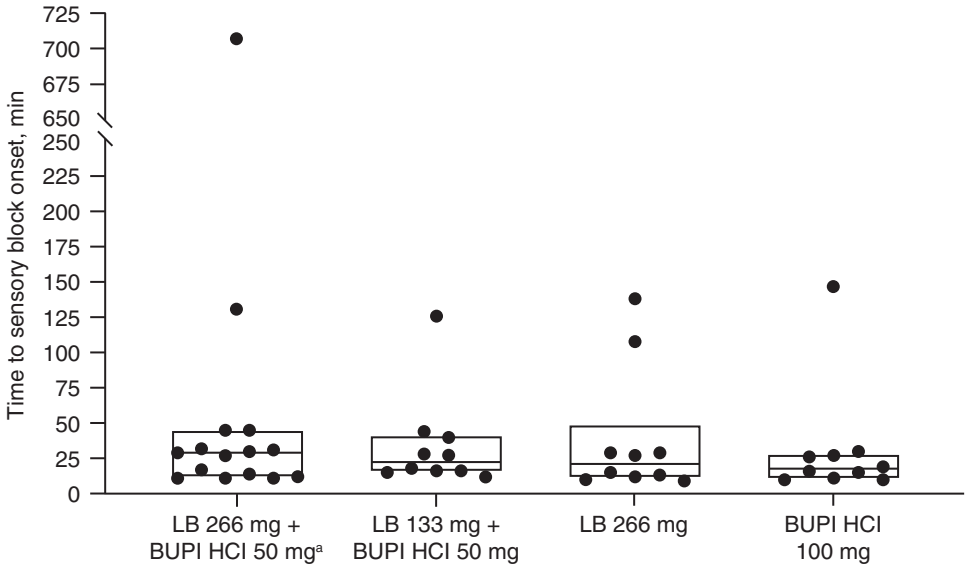

Figure 3. Time to onset of sensory block by cohort. The upper and lower boundaries of the boxes are the upper and lower quartiles. The horizontal lines inside the boxes are the median. [a]One participant did not have sensory block onset at the 2 h assessment but did at 12 h; given the lack of sensory block assessments between these time points, the specific timing of sensory block onset between 2 and 12 h could not be obtained for this participant. BUPI HCl, bupivacaine hydrochloride; LB, liposomal bupivacaine.

Table 3. Median Time to Onset and Duration of Motor Block by Cohort

	LB 266 mg + BUPI HCl 50 mg (n = 15)	LB 133 mg + BUPI HCl 50 mg (n = 10)	LB 266 mg (n = 10)	BUPI HCl 100 mg (n = 10)
Time to onset, median (95% CI), h	0.5 (0.3-0.8)	0.5 (0.2-0.8)	0.5 (0.2-0.5)	0.4 (0.2-0.5)
Duration, median (range), h	119 (58-147)	119 (59-144)	156 (71-193)	64 (23-144)

BUPI HCl, bupivacaine hydrochloride; CI, confidence interval; LB, liposomal bupivacaine.

cohorts given liposomal bupivacaine compared with the cohort receiving bupivacaine HCl 100 mg.

Motor and sensory block were delayed by ~15 to 30 min relative to bupivacaine plasma concentrations. Motor and sensory block responsiveness to bupivacaine was comparable, with half-maximal drug responses achieved at mean effect compartment concentrations of 34 ng/mL for motor block and 33 ng/mL for sensory block.

Safety

A total of 20 of 45 participants (44%) experienced at least one adverse event, the most common being nausea (Table 4). Most adverse events were mild to moderate in severity; nausea was the only adverse event observed in the study that was considered related to treatment. There were no serious adverse events, discontinuations due to adverse events, or on-study deaths reported in the study. No serious adverse events were reported in any cohort.

Exploratory Efficacy Analysis

Although pain scores were not formally compared statistically, the mean AUC for pain intensity scores from 24 to 96 h appeared numerically greater in the bupivacaine HCl 100 mg cohort than in the other cohorts (Table 5).

Discussion

Liposomal bupivacaine administered via popliteal sciatic nerve block resulted in plasma concentrations of bupivacaine <500 ng/mL, which is well below the 2000 ng/mL lower bound of the toxicity threshold.[9,11–14] The highest observed individual bupivacaine concentration was ~1200 ng/mL, which occurred in a participant given bupivacaine HCl 100 mg. The highest observed bupivacaine concentration in any participant given liposomal bupivacaine was ~800 ng/mL and occurred in a participant given liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg. Thus, all plasma bupivacaine concentrations were well below the toxicity threshold.[9]

In both liposomal bupivacaine + bupivacaine HCl cohorts, an early peak observed within an hour was followed by another peak between 24 and 65 h after administration. The initial differences in bupivacaine concentrations between the liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg cohort and the

Table 4. Overview of AEs (Safety Analysis Set)

	LB 266 mg + BUPI HCl 50 mg (n = 15)	LB 133 mg + BUPI HCl 50 mg (n = 10)	LB 266 mg (n = 10)	BUPI HCl 100 mg (n = 10)
Participants with ≥1 AE, n (%)	9 (60)	2 (20)	2 (20)	7 (70)
Maximum severity of AEs, n (% of cohort participants)				
Mild	8 (53)	2 (20)	1 (10)	6 (60)
Moderate	1 (7)	0	0	1 (10)
Severe	0	0	1 (10)	0
Participants with ≥1 treatment-related AE, n (%)	3 (20)	0	0	1 (10)
Most common AEs (>10% in any group), n (%)				
Nausea	6 (40)	0	1 (10)	3 (30)
Constipation	2 (13)	1 (10)	0	1 (10)
Dizziness	2 (13)	0	1 (10)	0
Headache	2 (13)	0	0	1 (10)

AE, adverse event; BUPI HCl, bupivacaine hydrochloride; LB, liposomal bupivacaine.

Table 5. Pain Intensity Scores by Cohort

	LB 266 mg + BUPI HCl 50 mg (n = 15)	LB 133 mg + BUPI HCl 50 mg (n = 10)	LB 266 mg (n = 10)	BUPI HCl 100 mg (n = 10)
AUC,[a] n	15	10	10	10
Mean (SD)	255 (172)	236 (171)	243 (177)	445 (172)
Median (min, max)	240 (24, 672)	222 (0, 618)	204 (0, 546)	438 (168, 696)

AUC, area under the plasma concentration versus time curve; BUPI HCl, bupivacaine hydrochloride; LB, liposomal bupivacaine; SD, standard deviation.
[a] AUC is from 24 to 96 h.

nonadmixed cohort at earlier time points (0-72 h) are due to the admixture with bupivacaine HCl as late concentrations were similar. Results with liposomal bupivacaine administered as popliteal sciatic nerve blocks are consistent with previous studies that report that bupivacaine plasma concentrations remain well below 2000 to 4000 ng/mL when liposomal bupivacaine is injected in other anatomic locations and via other routes of administration, with or without bupivacaine.[9,11–14]

Coadministration of liposomal bupivacaine 266 mg and bupivacaine HCl 50 mg resulted in two observed peaks in plasma bupivacaine concentration, similar to the pattern recently reported in a phase 3 study of liposomal bupivacaine administered alone (266 or 133 mg) via popliteal sciatic nerve block for bunionectomy.[15] While early peak bupivacaine concentrations differed between studies, because of admixture of bupivacaine HCl in the current study, late peak concentrations in cohorts receiving liposomal bupivacaine were similar to the phase 3 study.[15] In the current study, liposomal bupivacaine 266 mg alone did not produce a pronounced early plasma concentration peak, which is consistent with pharmacokinetics profiles reported for liposomal bupivacaine when administered via brachial plexus[11] and femoral nerve blocks.[18] However, although dissolution from the liposomes was slow, a small fraction of the administered liposomal bupivacaine dose was released immediately resulting in a biphasic disposition. This small fraction of immediate release from liposomal bupivacaine has been characterized previously and is thought to be due to a small amount of free bupivacaine being available in solution, injection shear forces, and/or changes in physicochemical properties.[19,20] Overall, the pharmacokinetic observations with liposomal bupivacaine in the current study were consistent with previous studies (Table S4) and support predictable liposomal bupivacaine pharmacokinetics when given alone or admixed with conventional bupivacaine.[9,11,12,15,21]

Sensory and motor block onset times were comparable in the bupivacaine HCl 100 mg and liposomal bupivacaine 266 mg cohorts, which differs from the phase 3 trial noted above, in which median onset of sensory block occurred later in participants given liposomal bupivacaine (~1 h) versus participants given bupivacaine HCl 50 mg alone (~30 min).[15] However, the current findings are supported by the exposure-response model, which suggested admixing bupivacaine HCl with liposomal bupivacaine resulted in higher early C_{max} without reducing time to onset of motor and sensory block. The observed differences in time to onset of sensory block between treatments may be partially

attributed to differences in study design, given that the phase 3 study was specifically designed to isolate the effects of the popliteal sciatic nerve block.[15]

Median sensory block durations in cohorts given liposomal bupivacaine ranged from 5 to 7 days, which was approximately twice as long as the duration observed with bupivacaine HCl 100 mg (<3 days). Interestingly, the median sensory block duration with bupivacaine HCl alone in the current study was much longer than previously reported durations of postsurgical analgesia following sciatic nerve block in more invasive foot procedures with bupivacaine HCl (~13[22] to 20 h[23]). Importantly, onset times and block durations for motor and sensory block were similar with 133 and 266 mg of liposomal bupivacaine when coadministered with bupivacaine HCl, indicating that the lower dose may be sufficient for sciatic nerve blocks. There was a temporal delay between bupivacaine plasma concentrations and motor and sensory block, which is likely attributable to the gradual distribution from the administration site to the pharmacodynamic effect site. Although brief, this delay may account for the similar onset times between the admixed and nonadmixed cohorts.

Liposomal bupivacaine administered alone had a similar safety profile as when admixed with bupivacaine HCl. Furthermore, the safety profile was consistent with other studies that evaluated liposomal bupivacaine in different routes of administration.[9,11–14] Nausea and constipation were the most common adverse events as in previous studies of liposomal bupivacaine.[9] Of note, the recent phase 3 trial of liposomal bupivacaine administered as popliteal sciatic nerve block included 133-mg and 266-mg doses of liposomal bupivacaine but did not evaluate admixture with bupivacaine HCl.[15] The similar safety profile of liposomal bupivacaine 266 mg + bupivacaine HCl 50 mg observed in the current study relative to bupivacaine HCl 50 mg alone, as in the recent phase 3 trial of liposomal bupivacaine,[15] suggests the liposomal bupivacaine 266 mg dose level admixed with bupivacaine may be safe for use in popliteal sciatic nerve block for lower extremity surgical procedures.

One major limitation of this study was that treatments were not randomly assigned and investigators were not blinded to treatment. However, it is unlikely that selection or measurement bias would considerably influence the pharmacokinetics results. It is possible, but perhaps unlikely, that participants had expectations that were based on the administered local anesthetic combinations that may have biased reports related to duration of action or complications. Another limitation was that the limited overall sample size (45 participants, including 10-15 participants per treatment cohort) may have limited the ability to detect potential complications; additionally, a greater proportion of participants were women. Finally, the current trial was not powered for clinical outcomes such as pain scores, and sensory block does not directly translate to postsurgical analgesia. Therefore, the efficacy and safety of liposomal bupivacaine 133 mg for popliteal sciatic nerve block was further investigated and established in a subsequent phase 3 study.[15]

Conclusions

Bupivacaine plasma concentrations were well below the toxic threshold range of 2000 to 4000 ng/mL with every tested combination of liposomal bupivacaine and/or bupivacaine HCl. Time to sensory block onset ranged from 18 to 29 min in all groups regardless of whether bupivacaine HCl was included. Block duration was approximately doubled with liposomal bupivacaine compared with bupivacaine HCl alone and lasted 5 to 7 days. The lower dose of liposomal bupivacaine (133 mg) was as effective as the higher dose (266 mg) in terms of sensory block onset and duration. The results of this study are generally consistent with previous data and suggest that popliteal sciatic nerve block duration is markedly prolonged by liposomal bupivacaine and that peak plasma bupivacaine concentrations are well below the toxic threshold. Current and previous[15] evidence thus supports the efficacy and safety of 133-mg liposomal bupivacaine for popliteal sciatic nerve blocks when given alone or admixed with bupivacaine HCl.

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Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study may be provided by the study sponsor upon reasonable request.

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Supplemental Information

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