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EXPERT OPINION

Liposome bupivacaine in peripheral nerve blocks and epidural injections to manage postoperative pain

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Introduction: The duration of postsurgical pain greatly outlasts the duration of analgesia (typically < 12 h) following single administration of traditional formulations of local anesthetics. Bupivacaine, one of the most widely studied and extensively used local anesthetics, is now available in a liposomal formulation that has shown promise of providing postsurgical analgesia for a duration of up to 72 h when administered as part of a peripheral (e.g., femoral) or neuraxial (e.g., epidural) nerve block. However, it is currently approved for administration in the surgical site.

Areas covered: This publication provides an overview of liposome bupivacaine and its potential utility in peripheral nerve blocks and epidural administration.

Expert opinion: The potential to provide postoperative analgesia lasting 3 days with a single administration at the time of surgery holds considerable promise. This modality could have distinct advantages over currently available techniques, such as continuous perineural local anesthetic infusion, as it would preclude the need for a catheter and pump. However, potential risks and benefits of liposome bupivacaine in peripheral and neuraxial nerve blocks must be further elucidated in surgical populations, and US Food and Drug Administration (FDA) approval must be granted for these indications. Until FDA approval is provided, the use of liposome bupivacaine in peripheral and neuraxial nerve blocks must be considered investigational.

Keywords: analgesia, epidural, liposome bupivacaine, peripheral nerve block, postoperative pain, regional anesthesia

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1. Introduction

Local anesthetics have a long history of use in the management of perioperative pain, dating back to the late nineteenth century. The first such use involved cocaine administration during eye surgery in 1884, and, although effective, cocaine was associated with considerable toxicities that prompted subsequent development of safer alternatives (**Figure 1**) [1,2]. Today, local or regional administration of anesthetics is integral to prevention of perioperative pain [3-8]. Ropivacaine, chloroprocaine, lidocaine, mepivacaine and bupivacaine are administered perioperatively via infiltration, peripheral or epidural (i.e., neuraxial) nerve block [9,10]. Of these, bupivacaine is one of the most widely studied and extensively used [3,10]. Favorable attributes of bupivacaine include high lipid solubility (which increases potency) and extensive protein-binding (which increases duration of action) [9,10]. Unfortunately, even bupivacaine – one of the longest-acting local anesthetics available – provides a duration of action (typically < 24 h) insufficient to provide adequate postoperative analgesia following a single-dose administration.

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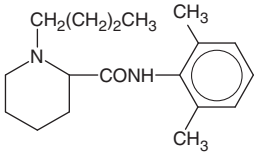
Box 1. Drug summary.

Drug name	Bupivacaine liposome injectable suspension (liposome bupivacaine)
Phase	IV
Indication	Single-dose infiltration into the surgical site to produce postsurgical analgesia
Pharmacology description	Liposome bupivacaine is a local anesthetic. Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing propagation of the nerve impulse and by reducing the rate of rise of the action potential
Route of administration	Liposome bupivacaine is indicated for administration in the surgical site. Other modes of administration are investigational
Chemical structure	
Pivotal trials	[18,23,26,30,33,48,49]

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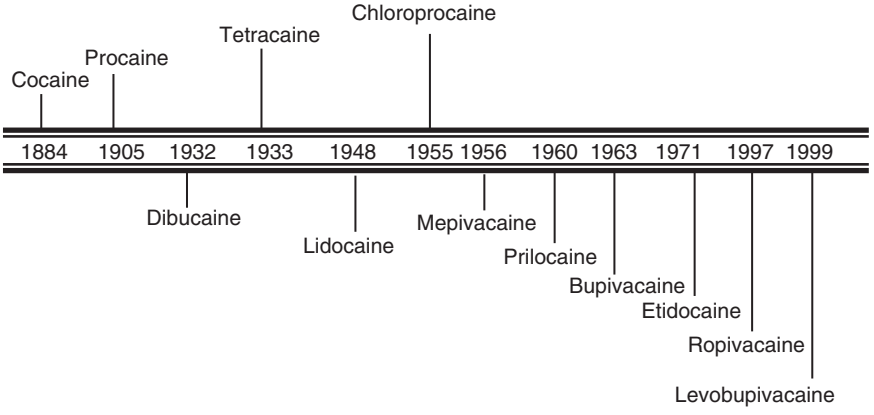

Figure 1. Chronology of the introduction of different anesthetics into clinical practice [2].
Original figure courtesy of David A. Scott, Melbourne, Australia, 2013.

Levobupivacaine, the S enantiomer of bupivacaine, was developed based on the belief that the pure S enantiomer would have less potential for toxicity than the R enantiomer and racemic mixture of bupivacaine [2,11]. However, the clinical relevance of this potential difference is unclear, as the safety profiles of bupivacaine and levobupivacaine appear to be very similar with standard/typical clinical usage [11].

The last few decades have seen attempts to extend local anesthetic duration of action. Manipulation of the molecular structure of anesthetics, such as tetraethylammonium, led to extended activity but was also associated with severe neurotoxicity in mammals [12]. Relatively poor or variable results have been reported for strategies such as adding dextran, carbonating the anesthetic or combining faster-acting with longer-acting anesthetics (e.g., chloroprocaine with bupivacaine). Currently, the most commonly used technique is the addition of additives such as epinephrine [10] and clonidine [13]. However, at present, there is no approved strategy to reliably extend the duration of action associated with single-injection peripheral or epidural nerve block to > 24 h. Therefore, the current gold standard for extending the duration of postsurgical analgesia with local anesthetics involves use of continuous peripheral or epidural nerve blocks in which a catheter is inserted percutaneously, adjacent to a target nerve or in the epidural space, and local anesthetic is subsequently infused for multiple days [14,15].

A relatively new strategy for prolonging the duration of action is to incorporate local anesthetic drugs into liposomes by either encapsulating them in the aqueous space or intercalating them into the lipid bilayers, thereby slowing the release of the drug [16,17].

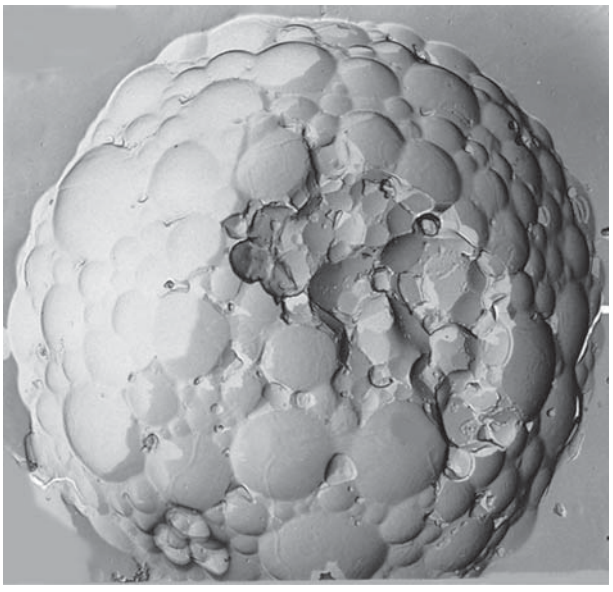

Figure 2. Electron micrograph image of liposome bupivacaine [19].
Richard BM, Ott LR, Haan D, et al. Expert Opin Investig Drugs 2011;20(10):1327-1341, copyright ©2011, Informa Healthcare. Reproduced with permission of Informa Healthcare.

2. Overview of bupivacaine liposome injectable suspension

Bupivacaine liposome injectable suspension (EXPAREL; Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA) (**Box 1**) consists of multivesicular liposomes in a honeycomb-like formation (DepoFoam) with numerous aqueous chambers that contain bupivacaine (**Figure 2**) [18,19]. The proprietary DepoFoam technology [20], which provides steady, reliable and prolonged drug release, is well established, having been used to encapsulate multiple other medications [21]. In this report, the milligram dose of liposome bupivacaine is expressed as the free base (e.g., 266 mg of bupivacaine base is chemically equivalent to 300 mg of bupivacaine HCl). Liposome bupivacaine is approved by the US Food and Drug Administration (FDA) for single-dose administration in the surgical site to produce postsurgical analgesia in adults [20].

In 10 double-masked, randomized, controlled trials, liposome bupivacaine was administered at single doses ranging from 66 to 532 mg as wound infiltration in 823 subjects undergoing hernia repair, total knee arthroplasty, hemorrhoidectomy, breast augmentation or bunionectomy [22]. A pooled analysis of data from these studies showed that liposome bupivacaine was associated with a significantly longer time to first postoperative use of opioid medications (median, 9.3 h) compared with either placebo (3.6 h, $p < 0.0001$) or bupivacaine hydrochloride (HCl) (6.4 h, $p = 0.013$). Another analysis conducted by Dasta *et al.* [23] focused on pooled data from study subjects receiving liposome bupivacaine at doses up to and including the highest FDA-approved dose (266 mg) compared with bupivacaine HCl. In this analysis, the mean cumulative pain intensity score in subjects receiving liposome bupivacaine was 283 compared with 329 in those receiving bupivacaine HCl ($p = 0.039$). Administration of liposome bupivacaine was also associated with longer median time to first administration of postsurgical opioid rescue (9.9 h) and total amount of opioids consumed after surgery (12.2 mg) versus bupivacaine HCl (2.7 h and 19 mg, respectively; $p < 0.0001$ for both comparisons). Data regarding the effectiveness of single-dose administration into the transversus abdominis plane (TAP) to cover the abdominal surgical area [24,25] have also been reported previously.

Liposome bupivacaine has been well tolerated in studies conducted to date with a safety profile similar to that of bupivacaine HCl [22]. Across 10 clinical trials, 62% of subjects treated with liposome bupivacaine, 75% of those treated with bupivacaine HCl and 43% of placebo controls experienced at least one adverse event (AE), most of which were mild or moderate in severity [26]. Of the 823 subjects who received liposome bupivacaine, 22 subjects reported serious AEs; none of the serious AEs were considered treatment-related by study investigators [26]. The authors who reported these safety data noted several limitations to their analysis: the safety data were compiled from a relatively small number of subjects in studies where liposome bupivacaine was administered in the surgical site. Also, pooling of safety data was not prespecified in the protocols for the individual studies, and statistical analyses of between-group differences were not conducted.

Cardiotoxicity and impaired wound healing are theoretical concerns with use of local anesthetics [18,27,28]. An analysis of the 10 randomized wound infiltration studies of liposome bupivacaine found no evidence of impaired short- or long-term wound healing [28]. Cardiac AEs, consisting of bradycardia and tachycardia, occurred in < 1% of subjects, where all were mild or moderate and did not require intervention [26]. In one randomized, double-masked Phase II study of liposome bupivacaine (133 – 532 mg) vs bupivacaine HCl administered via wound infiltration in 138 subjects undergoing total knee arthroplasty, electrocardiograms were assessed through 96 h postdose [18]. There were no signals of increased cardiac risk with liposome bupivacaine, even in three subjects who had elevated plasma levels of bupivacaine resulting from suspected intravascular administration. Overall, incidences of reported AEs related to the cardiac, psychiatric and nervous system organ classes were similar in treatment arms receiving liposome bupivacaine and bupivacaine HCl [26], and no clear signs of cardiac or neurotoxicity have been observed to date [18].

Based on the known benefits and long history of local anesthetics in various perioperative settings, liposome bupivacaine potentially has utility in other forms of regional anesthesia. Recent studies have begun to evaluate liposome bupivacaine use in peripheral nerve blocks and epidural administration.

2.1 Peripheral nerve blocks

2.1.1 Preclinical investigations

Preclinical toxicology investigations of liposome bupivacaine peripheral nerve blocks were conducted in rabbits and dogs [29]. Liposome bupivacaine, bupivacaine HCl or 0.9% sodium chloride injection (saline control) were administered as bolus injections into the brachial plexus nerves of the left shoulder. The only noteworthy effect was mild granulomatous inflammation of adipose tissue at the roots of the brachial plexus nerves, which occurred in 8 of 24 rabbits and 7 of 24 dogs. This was considered a normal foreign body response to the liposomes. Overall, there were no local signs of bupivacaine toxicity observed during the studies.

2.1.2 Healthy volunteers

Two studies of liposome bupivacaine peripheral nerve block have been performed in healthy adults. One study evaluated dose response associated with liposome bupivacaine 0 – 80 mg administered per side for ultrasound-guided bilateral femoral nerve blocks in 14 adult volunteers [30]. Motor effects of study drug were assessed via measurement of maximum voluntary isometric contraction (MVIC) of quadriceps femoris muscles; sensory effects were measured via evaluation of tolerance to transcutaneous electrical stimulation. There was a wide variation in interindividual response, and paradoxically, there was an inverse dose-related effect on motor and sensory function, as measured by quadriceps MVIC and tolerance to cutaneous electrical current. In other words, the higher the dose, the lower the observed effect. With each milligram increase in bupivacaine, MVIC increased by a mean of 0.09% (standard error [SE] = 0.03; 95% confidence interval [CI]: 0.04 – 0.14; p = 0.002) and tolerance to cutaneous current decreased by 0.03 mA (SE = 0.01; 95% CI: -0.04 to -0.02; p < 0.001). It is noteworthy that two subjects with anomalous dose–response profiles may have either experienced a placebo effect or intentionally falsified responses; with exclusion of these two individuals, the correlation between dose and sensory block was nonsignificant and the correlation between dose and motor blockade reversed to the expected direction. In sum, liposome bupivacaine generally resulted in a partial motor block; regarding sensory block, subjects who received higher doses had a more consistent response pattern of requiring greater transcutaneous electrical stimulation current to reach slight discomfort (sensory block) than did subjects who received lower doses. The only reported AE was transient pruritus and erythema at the injection site during the first few days after administration in one participant (on a side receiving normal saline placebo). This event resolved without treatment and was deemed unrelated to the study medication.

The second study, as yet unpublished, was a single-center, randomized, double-masked, dose-escalation study in 36 healthy young men who received either bupivacaine HCl at a dose of 75 mg or liposome bupivacaine at escalating doses (66, 111, 133 or 155 mg) (E. Onel, Pacira Pharmaceuticals, written communication, 25 June 2013). The primary objective was to assess dose-related sensory nerve block; pharmacokinetic (PK) parameters were also assessed. Study drug was administered as a single injection to block the deep peroneal, superficial peroneal and saphenous nerves. At all doses, peak plasma concentration (C_{max}) was reached within 30 min after study drug administration and was followed by a multiphasic decline with secondary peaks at ~ 18 and 48 h (**Figure 3A**). C_{max} increased in an approximate dose-proportional manner following administration of liposome bupivacaine and C_{max} was lower with liposome bupivacaine than bupivacaine HCl. Mean total exposure, as reflected in the area under the plasma concentration–time curve from time of dosing to the time of last quantifiable concentration ($AUC_{0\text{-}t\text{last}}$), was greater following the four liposome bupivacaine doses (1976, 2635, 3949 and 3857 ng·h/ml, respectively) compared with bupivacaine HCl (1889 ng·h/ml). Mean half-life was longer (26, 23, 53 and 35 h) for the four liposome bupivacaine doses, respectively, compared with bupivacaine HCl (13 h), but the secondary spikes in bupivacaine concentration following administration of liposome bupivacaine may have made determination of half-life unreliable. Sensory blockade (assessed using cold, warmth and vibration sensory thresholds) was prolonged following administration of liposome bupivacaine, particularly at the highest dose (155 mg), compared with bupivacaine HCl, with effects lasting through 72 h after administration (**Figure 3B – D**). After administration of liposome bupivacaine, participants exhibited dose-related impairment in sensitivity to pinprick at the top of the foot;

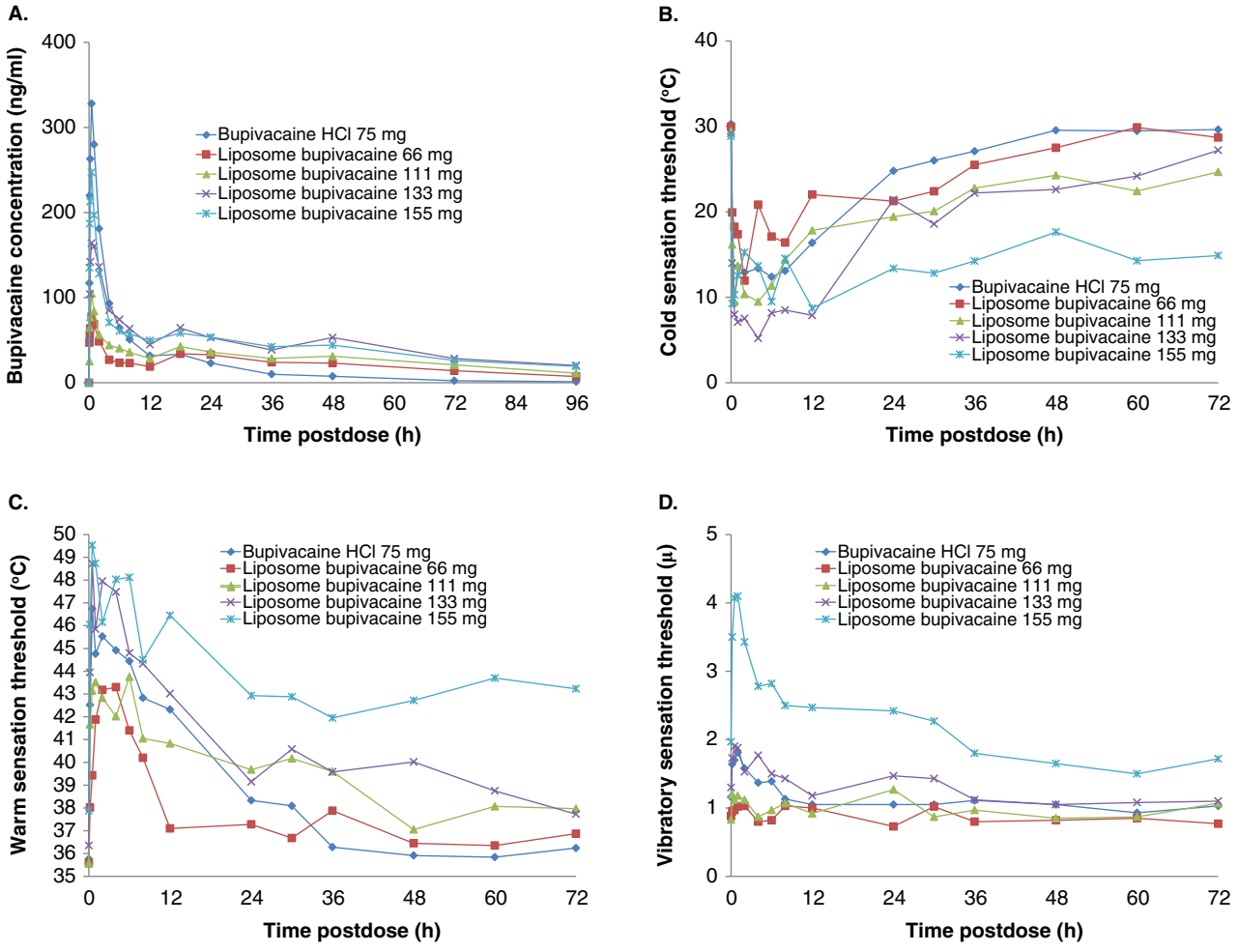

Figure 3. Femoral block with bupivacaine HCl 75 mg (0.5%) and liposome bupivacaine 66, 111, 133 or 155 mg in healthy male volunteers: (**A**) mean plasma concentration–time curve of bupivacaine (**B**) mean cold sensation threshold; (**C**) mean warm sensation threshold; (**D**) mean vibratory sensation threshold.

the majority of subjects retained sensation at the inside and outside of the foot.

2.2 Surgical populations

2.2.1 Surgical populations: TAP

Use of liposome bupivacaine for TAP field blocks has been investigated in two prospective, nonrandomized, open-label studies: one involving robot-assisted prostatectomy (n = 24) [24] and one in the setting of open abdominal hernia repair (n = 12) [25]. In the robotic prostatectomy study, subjects received TAP infiltration with liposome bupivacaine 266 mg in 20 ml (n = 12) or 40 ml (n = 12) of diluent immediately after surgery [24]. Mean subject-reported pain intensity scores, assessed using an 11-point numeric rating scale (0 = no pain; 10 = worst possible pain), remained ≤ 3 in both treatment groups beginning at 6 h after surgery through 96 h post-surgery. Liposome bupivacaine was well tolerated (no treatment-related AEs were reported) and all subjects reported that they were satisfied or extremely satisfied with their pain control.

Feierman *et al.* [25] assessed liposome bupivacaine 266 mg via TAP infiltration in 13 subjects undergoing umbilical hernia repair. In this study, mean pain intensity scores remained < 3 on a numeric rating scale (0 = no pain; 10 = worst possible pain) for at least 120 h following surgery; the TAP infiltration failed in one subject who had a pain intensity score of 10 at 4 h and was admitted to a hospital overnight for pain control. Most subjects (77%) reported that they were satisfied or extremely satisfied with postoperative pain control at discharge. There were no AEs reported in this study.

2.2.2 Surgical populations: peripheral nerve block

A Phase II, multicenter, randomized, double-masked, dose-escalating/de-escalating study was conducted to evaluate the safety, efficacy and PK of liposome bupivacaine (155, 199 and 310 mg) ankle nerve blocks versus bupivacaine

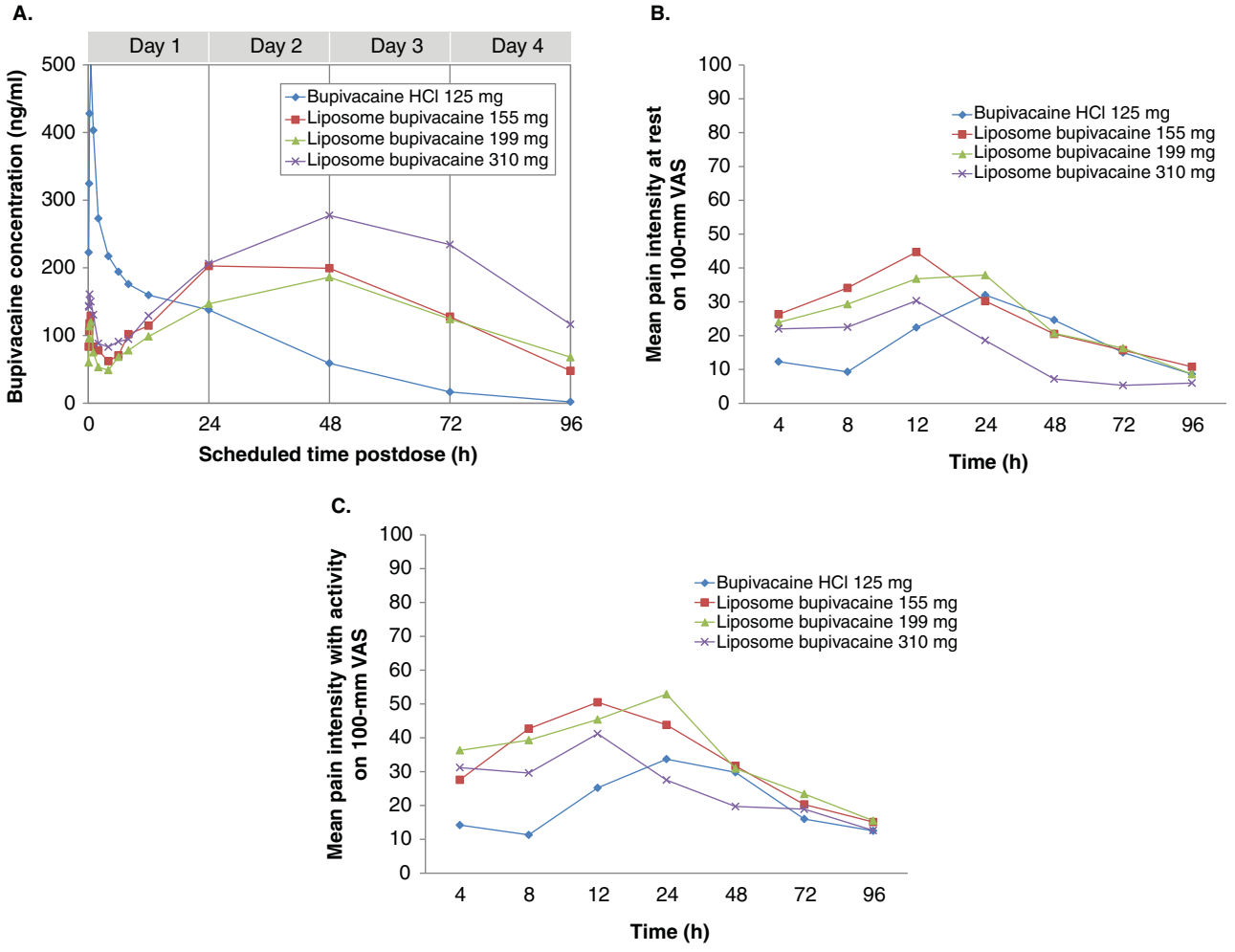

Figure 4. Ankle block with bupivacaine HCl 125 mg and liposome bupivacaine 155, 199 and 310 mg in subjects undergoing bunionectomy: (**A**) mean plasma concentration–time curve of bupivacaine; (**B**) mean pain intensity scores on 100 mm VAS at rest; and (**C**) with activity.

HCl (125 mg) for management of postsurgical pain in 58 adults undergoing bunionectomy (E. Onel, Pacira Pharmaceuticals, written communication, 25 June 2013). Nerve blocks consisted of five injections through three injection sites targeting the posterior tibial, sural, deep peroneal, superficial peroneal and saphenous nerves. PK analyses showed that liposome bupivacaine was associated with significantly greater AUC ($p \leq 0.01$ for each dose level of liposome bupivacaine vs bupivacaine HCl) and lower C_{max} ($p \leq 0.004$ vs bupivacaine HCl; **Figure 4A**), and approximately three- to fourfold longer mean half-life (31 – 67 h) compared with bupivacaine HCl (11 h). Pain intensity at rest and with activity was assessed using a 100 mm visual analog scale (VAS; 0 = no pain; 100 = most severe pain imaginable). Mean pain intensity scores at rest and with activity were lower in the bupivacaine HCl group than the three liposome bupivacaine groups through the first 12 h after surgery; however, at later time points through 96 h after surgery, the liposome bupivacaine 310 mg group had similar or lower VAS scores at rest and with activity than the bupivacaine HCl group (**Figure 4B** and **C**). Most subjects (> 90% in each treatment group) used supplemental pain medication (opioid or non-opioid) after surgery, and liposome bupivacaine did not lengthen the time to first use of supplemental analgesics or the total amount of opioids consumed. From 48 through 96 h, a smaller proportion of subjects in the liposome bupivacaine 310 mg group took opioids compared with bupivacaine HCl, although this difference was not statistically significant at 96 h. For all treatments, pain control was rated by most subjects and study personnel as good or very good.

The most common AEs in the liposome bupivacaine group were gastrointestinal (nausea, constipation and vomiting); none of these AEs were considered treatment-related by the investigator. Four subjects in the liposome bupivacaine

Table 1. PK and PD parameters of epidurally administered liposome bupivacaine or bupivacaine HCl.

	Liposome bupivacaine			Bupivacaine HCl
	89 mg (n = 8)	155 mg (n = 8)	266 mg (n = 7)	50 mg (n = 6)
PK parameters				
C_{max}, mean (SD), ng/ml	120 (47)	134 (54)	250 (64)	300 (78)
T_{max}, median (min-max), h	7 (0.5 – 16)	24 (2 – 24)	24 (8 – 48)	0.7 (0.5 – 0.9)
$AUC_{0\text{-}tlast}$, mean (SD), h·ng/ml	4064 (1325)	6387 (1708)	13,198 (3996)	1960 (414)
$AUC_{0\text{-}\infty}$, mean (SD), h·ng/ml	4151 (1312)	6565 (1679)	13,954 (4336)	1961 (414)
$t_{1/2}$, mean (SD), h	16 (6)	14 (5)	19 (8)	6 (1)
PD parameters				
Any motor blockade at any time through 96 h, n (%)	0	2 (25)	4 (57)	6 (100)
Duration of motor blockade, median,* h	0	0	1	2.8
Median time to full motor recovery,‡ h	–	2.9	3	4
Loss of ability to ambulate freely at 4 h, n (%)	0	7 (88)	2 (29)	4 (67)
Duration of ambulatory deficit, median,* h	0	2.1	0	1.5
Time to recovery of ability to ambulate freely, median,‡ h	–	6.1	6.2	6.2

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*Includes all subjects, whether or not they experienced motor blockade or lost the ability to ambulate freely.

‡Includes only subjects who experienced motor blockade or lost their ability to ambulate freely.

$AUC_{0\text{-}\infty}$: Area under the plasma concentration–time curve from time of dosing to infinity; $AUC_{0\text{-}tlast}$: Area under the plasma concentration–time curve from time of dosing to the time of last quantifiable concentration; C_{max}: Peak plasma concentration; PD: Pharmacodynamics; PK: Pharmacokinetics; SD: Standard deviation; $t_{1/2}$: Elimination half-life; T_{max}: Time to peak plasma concentration.

groups experienced cardiac AEs (right bundle branch block, first degree atrioventricular block, bradycardia and sinus tachycardia), although all were considered by the investigators to be unrelated to the study drug. No cardiac AEs were reported in the bupivacaine HCl group. The only serious AE (prolonged immobility) occurred in a subject who received liposome bupivacaine 199 mg, but this event resolved and was considered unlikely to be related to the study drug. There were no treatment discontinuations due to AEs.

A Phase II, open-label, randomized, parallel-group dose-finding study comparing liposome bupivacaine 66 or 133 mg, placebo or epidural bupivacaine HCl for intercostal peripheral nerve block was initiated in subjects undergoing posterolateral thoracotomy (E. Onel, Pacira Pharmaceuticals, written communication, 25 June 2013). This study was terminated after only 3 of the intended 45 subjects were enrolled for reasons unrelated to safety, pursuant to a business decision on the part of the sponsor company at the time.

2.3 Ongoing studies

Other studies investigating the use of liposome bupivacaine in peripheral nerve block are ongoing. A randomized, double-masked, placebo-controlled, two-part Phase II/III study is investigating liposome bupivacaine for ultrasound-guided femoral nerve block in subjects undergoing total knee arthroplasty [31]. In part 1, ~ 100 subjects (25 per treatment arm) will receive liposome bupivacaine 66, 133 or 266 mg or placebo. In part 2, about 180 subjects (90 per treatment arm) will receive the most appropriate dose of liposome bupivacaine identified in part 1 of the study or placebo. Another randomized, double-masked, placebo-controlled, Phase III study is evaluating liposome bupivacaine versus placebo for intercostal nerve block in about 180 subjects undergoing posterolateral thoracotomy [32]. In this study, subjects will receive a total of 266 mg divided between three nerves. Primary efficacy outcome measures in both studies include cumulative pain intensity scores through 72 h post-surgery, total postsurgical opioid consumption and time to first opioid use. Completion of both studies is anticipated before the end of 2013.

2.4 Epidural administration

Liposome bupivacaine for epidural administration is still in early phases of investigation. Preclinical assessments showed no apparent toxicity in rats or dogs which were given epidural liposome bupivacaine (E. Onel, Pacira Pharmaceuticals, Inc., written communication, 25 June 2013). In a study of rats given liposome bupivacaine alone, bupivacaine HCl, lidocaine/epinephrine followed by liposome bupivacaine 15 min later, or saline (placebo), 37% of the animals treated with epidural bupivacaine HCl died of lethal overdose; no such deaths occurred with liposome bupivacaine alone, but two animals died after receiving lidocaine/epinephrine followed by liposome bupivacaine. A similar study was carried out in beagle dogs. In this study, impairment in hind limb function occurred solely on the day of administration in four of six animals treated with bupivacaine HCl, five of six animals treated with lidocaine/epinephrine followed by liposome bupivacaine but none of the dogs given liposome bupivacaine alone. In

addition, dogs treated with bupivacaine HCl or lidocaine/epinephrine plus liposome bupivacaine exhibited a slight prolongation of activated partial thromboplastin time that was not observed in animals treated with liposome bupivacaine alone.

The PK and pharmacodynamics (PD) of epidural liposome bupivacaine were evaluated in a Phase I, randomized, double-masked, dose-escalating study in 30 healthy volunteers [33]. Sequential cohorts were treated with 89, 155 or 266 mg of liposome bupivacaine or 50 mg of bupivacaine HCl (**Table 1**). For each cohort, 20 ml of study drug was injected into the lumbar intervertebral space (L3-L4) via an epidural catheter. Compared with bupivacaine HCl, liposome bupivacaine had a significantly greater ($p < 0.001$) area under the plasma bupivacaine concentration–time curve from baseline to either last plasma sample ($AUC_{0\text{-}t\text{last}}$) or infinity ($AUC_{0\text{-}\infty}$). Elimination half-life of bupivacaine was about threefold longer for liposome bupivacaine versus bupivacaine HCl. Although between-group statistical calculations were not performed, a numerically smaller proportion of subjects treated with liposome bupivacaine experienced any motor blockade in the 96-h period after administration (26% [6 of 23] of those receiving liposome bupivacaine vs 100% [6 of 6] of those receiving bupivacaine HCl), and motor blockade lasted for a shorter duration compared with bupivacaine HCl (medians were 0, 0 and 1 h in the liposome bupivacaine 89, 155 and 266 mg groups, respectively, vs 2.8 h for bupivacaine HCl). All subjects lost sensitivity to cold, and all except for one subject in the liposome bupivacaine 155 mg group lost sensitivity to pinprick; duration of numbness to pinprick was about three times longer (median 35.6 vs 11.5 h) and insensitivity to cold was about six times longer (median 68.7 vs 11.6 h) in subjects who received liposome bupivacaine 266 mg versus those who received bupivacaine HCl.

Both liposome bupivacaine and bupivacaine HCl given via epidural administration were well tolerated. The most common AEs were injection-site pain (83% with either treatment) and headache (21% with liposome bupivacaine; 0 with bupivacaine HCl). All AEs were mild to moderate. There were no serious AEs, and there were no study discontinuations resulting from AEs.

3. Risks of myotoxicity and neurotoxicity with local anesthetics

Anesthetics work by directly interacting with voltage-gated Na^+ channels, reducing membrane permeability to Na^+, thereby blocking conduction of nerve impulses [34]. To varying extents, local anesthetics administered at appropriate concentrations may block both sensory and motor function in the innervated area [34]. High doses of local anesthetics have the potential to induce myotoxicity and neurotoxicity [2]. Although myotoxicity has been observed in laboratory studies of local anesthetics [35-37], clinically relevant myotoxicity appears to be rare [38]. Neuronal toxicity has been reported with all local anesthetics, although relative risk from one to another [39], and it appears to be a function of drug concentration and exposure [40-42].

McAlvin *et al.* [43] recently pointed to the risk of myotoxicity and neurotoxicity as a major factor limiting the use of various controlled release formulations of local anesthetics. Therefore, it is noteworthy that there has been no evidence of myotoxicity or neurotoxicity associated with liposome bupivacaine in clinical studies that have been conducted to date. Further, the study of epidural administration of liposome bupivacaine versus bupivacaine HCl found that subjects who received liposome bupivacaine experienced a longer duration of sensory block with less effect on motor function [33].

4. Conclusion

Bupivacaine, one of the most widely used and well-established local anesthetics, is now available in a liposomal formulation. PK studies show that liposome bupivacaine exhibits prolonged release and produces a more sustained sensory blockade compared with standard bupivacaine whether used for wound infiltration, peripheral nerve blocks or for epidural administration. Based on the known benefits and long history of local anesthetics in various perioperative settings, liposome bupivacaine potentially has utility in other forms of local or regional anesthesia beyond the FDA-approved indication for single-dose wound infiltration. Liposome bupivacaine peripheral nerve blocks resulted in sensory and motor blockade lasting for over 24 – 72 h in most healthy volunteers. In subjects undergoing bunionectomy, liposome bupivacaine peripheral nerve block provided a degree of analgesia similar to that of bupivacaine HCl but with longer lasting analgesic effect of up to 72 h. Future randomized, double-masked studies should continue to explore liposome bupivacaine for peripheral nerve blocks and epidural administration in surgical patients. The optimal dose of liposome bupivacaine in peripheral nerve blocks and for epidural administration has not yet been determined.

5. Expert opinion

The key finding from research done to date is that duration of analgesia following a single injection of liposome bupivacaine for peripheral or epidural nerve block outlasts standard bupivacaine HCl, which is currently the longest-acting local anesthetic approved by the FDA for these modalities. Since many surgical procedures result in postoperative pain that lasts much longer than 24 h, liposome bupivacaine clearly has potential to replace the currently available local anesthetic formulations.

It is noteworthy that continuous peripheral nerve blocks (also termed perineural local anesthetic infusion) using

currently available local anesthetics to provide extended duration analgesia are already approved by the FDA [14,15]. In addition, there is a considerable amount of data from prospective research involving perineural local anesthetic infusion that documents the optimal management and benefits of this analgesic technique [15]. However, the possibility of a single-injection peripheral nerve block providing > 3 days' duration of analgesia has multiple theoretical benefits over a continuous infusion. The potential advantages include the obviation of catheter insertion training [44], infusion pump expense [45], management of the infusion itself and the possibility of catheter dislodgement [14], as well as decreased risks such as infection and catheter-related hematoma formation [46]. Until liposome bupivacaine receives FDA approval for use in peripheral nerve blocks and the techniques are directly compared, the advantages will remain speculative.

The current limitations in the available data are clear. The potential risks and benefits of liposome bupivacaine in peripheral and neuraxial nerve blocks must be further elucidated in surgical populations using randomized, controlled clinical trials. One potential limitation in using a single injection of liposome bupivacaine is the inability to titrate the dose to the effect desired. The ability to 'remove' excess drug in cases where unwanted sensory or motor block occurs after the local anesthetic has already been administered has not been studied. Similarly, it is unknown if there are limits to the ability to 'add' more drug to liposome bupivacaine in the case of inadequate analgesia. Additionally, the optimal dose/volume/concentration of a single injection that provides adequate analgesia while minimizing unwanted sensory and/or motor block has not yet been determined. Preliminary investigations suggest that the analgesia-to-motor block ratio is extremely favorable for liposome bupivacaine, even when administered at high doses for peripheral and epidural nerve blocks. Another potential limitation centers on the use of liposome bupivacaine for intraoperative anesthesia, as opposed to postoperative analgesia. Traditional formulations of local anesthetics administered with a sufficient dose in a single injection provide dense anesthesia, which allows surgery to be performed without use of a general anesthetic. Preliminary investigations of liposome bupivacaine administered at the doses most likely to be utilized do not provide such dense anesthesia. However, if the extensive potential postoperative analgesic benefits are realized for liposome bupivacaine, it is probable that practitioners will use other anesthetics (e.g., a 'spinal') to allow the use of liposome bupivacaine.

Currently, several trials are ongoing in peripheral and neuraxial nerve block settings. Positive results from these studies may lead to FDA approval for use within these application techniques. Other future areas of investigation for liposome bupivacaine may include intra-articular administration and use in patients with chronic pain.

In conclusion, the results of preliminary studies suggest that liposome bupivacaine administered as a single injection for peripheral or epidural nerve block results in a partial sensory and motor blockade that could provide postoperative analgesia lasting for > 3 days. The author emphasizes that this bupivacaine formulation is currently approved by the FDA for infiltration of surgical wounds. Therefore, multiple Phase III trials involving subjects undergoing various surgical procedures is the next logical step. If such trials confirm the preliminary findings, and if the FDA subsequently approves liposome bupivacaine for use in peripheral and/or epidural nerve blocks, healthcare providers will have a very promising new analgesic option – one that combines the relative ease of a single injection of local anesthetic with the dramatic benefits of potent, site-specific, multiday analgesia. Considering the hundreds of millions of surgical procedures performed annually worldwide [47], the potential of liposome bupivacaine is remarkable.

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