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Liposomal bupivacaine and novel local anesthetic formulations

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Novel preparations allowing for the extended duration of action of local anesthetics have many clinically relevant benefits. With regard to this, the development of liposomal bupivacaine has the

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potential to significantly impact patient care by improving perioperative pain control. The unique liposomal bilayer that encapsulates bupivacaine allows for a sustained release of local anesthetic for up to 72 h after a single use and can significantly decrease postoperative opioid consumption. SABER-bupivacaine is another depot formulation that helps in sustained release of bupivacaine from an encapsulated bupivacaine in a biodegradable sucrose acetate isobutyrate biolayer. HTX-011 is an investigational extended-release local anesthetic formulation currently undergoing Phase 3 clinical trials. HTX-011 is composed of a bioerodible polymer with bupivacaine and low-dose meloxicam in which the polymer undergoes hydrolysis and allows for sustained release of bupivacaine and meloxicam for 3 days. The present investigation reviews pharmacologic considerations related to the formulation of liposomal bupivacaine, current FDA-approved indications for its use, and future extended-release local anesthetic formulations currently under investigation.

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Introduction

Multimodal analgesic regimens are an integral component of perioperative pain management. Poorly controlled pain in the postoperative period is associated with several unfavorable outcomes including decreased patient satisfaction, longer hospital length of stays, delayed initiation of physical therapy and rehabilitation, and an increased incidence of medication-induced adverse effects [1]. Evidence-based data now clearly support the use of a variety of different medications that work synergistically in the preoperative, intraoperative, and postoperative periods to help limit pain after surgery. Additive and/or synergistic effects between medications can help decrease the total amount of medication given and therefore also help limit adverse effects such as respiratory depression and toxicity. Multimodal regimens generally consist of oral and intravenous medications combined with regional techniques with the goal to be opioid sparing. One of the biggest breakthroughs relevant to regional anesthesia is the development of liposomal bupivacaine. Liposomal bupivacaine allows for a slow and sustained release of local anesthetic at the intended site of action without the need for a perineural catheter. The present investigation, therefore, reviews the most current evidence relevant to liposomal bupivacaine use and describes local anesthetic formulations currently under development for future clinical use.

Overview of delivery mechanisms

The delivery of local anesthetics using encapsulating agents is a desirable alternative, as it provides a system for sustained release and subsequently results in enhanced analgesia. Through encapsulation, high doses of local anesthetics can be safely delivered to the site of action and slowly released over a prolonged period. Ideal encapsulating agents are biodegradable with nontoxic byproducts, provide controlled drug release, and are eliminated by normal metabolic pathways. Examples of encapsulating agents include liposomes, lipospheres, and polymeric microspheres and nanospheres [2–4].

Liposomes are vesicular carriers composed of a lipid bilayer that encompasses an aqueous core. Examples of common lipid bilayer components include phospholipids and cholesterol. The lipid bilayer serves as a reservoir for lipid-soluble drugs, whereas the aqueous interior is suitable for hydrophilic drugs such as local anesthetics. The duration of analgesia is dependent on the composition of the liposome (i.e., size and number of lipid bilayers), whereas the rate of drug release is dependent on bilayer permeability [2–4]. Types of liposomes include unilamellar vesicles (small and large), multilamellar vesicles, and multivesicular vesicles (MVL). Unilamellar vesicle liposomes

consist of a singular lipid bilayer enclosing an internal aqueous space, while MVL have coaxial bilayers. MVL are configured by an aggregate of multiple nonconcentric bilayers and aqueous sacs, which visibly appear like a honeycomb. The addition of local anesthetics to this honeycomb matrix results in a longer duration of action than unilamellar vesicles or free drug administered in the epidural space. The prolonged effects of MVL-encapsulated local anesthetics are attributed to the redistribution of drug within the matrix after the initial burst release. As the lipid bilayers continue to degrade, the drug is released from the exposed aqueous sac, followed by a second, less concentrated burst release. The bimodal burst release with intermediate sustained drug release prolongs anesthetic activity for several days [2,3,5].

However, the benefits of liposome formulations are also met with challenges. In addition to the high cost and complexity of drug production, encapsulated drugs have been reported to leak secondary to oxidation, hydrolysis, and destabilization of the liposome. Neurotoxicity attributed to liposome metabolite compounds can occur; however, the specific reaction, degree of severity, and incidence are unknown. When compared with bupivacaine HCl, the incidence of tissue reaction (i.e., myotoxicity) to liposomes was similar [3–5]. Bupivacaine is presently the only local anesthetic commercially available using MVL encapsulation [4].

Lipospheres are microparticles composed of a single phospholipid layer that entraps a hydrophobic triglyceride or fatty acid core that contains the respective drug. Like liposomes, liposphere formulations yield delayed drug release and minimal toxicity. Lipospheres are also desirable because the manufacturing process is less complex. The stability of bupivacaine formulation has also been improved with the use of synthetic phospholipids and the addition of carboxymethylcellulose. In animal studies, bupivacaine lipospheres produced 1–3 days of dose-dependent anesthetic activity. However, because it binds to the lipid surface, the drug is easily released from the encapsulating matrix [2–4].

Polymeric particles (e.g., microspheres and nanospheres) are prepared from biodegradable synthetic hydrophobic polymers, which include poly (lactic acid), poly (glycolic acid), or poly (lactic-co-glycolic acid) (PLGA). These polymer-based encapsulating agents allow for controlled and sustained drug release when prepared as either a solid polymer matrix or a hydrophobic capsule with a polymer shell. Local anesthetics are incorporated into the polymer matrix through emulsification with appropriate organic solvents. Compared to aqueous-based encapsulating agents, microspheres and nanospheres can achieve a higher drug loading resulting in a prolonged duration of action. However, it is suggested that larger particles also have a reduced degree of drug binding, which subsequently promotes a faster rate of drug release. Bupivacaine entrapped in PLGA microspheres produced pain relief for 3–4 days compared to that of 4–5 h after administration of nonencapsulated bupivacaine HCl. Data suggest that co-administration of dexamethasone can further extend the duration of nerve block [2–4]. Potential adverse effects of polymeric formulations include the development of acute and/or chronic inflammation. Notably, the incidence of myotoxicity is demonstrated to be higher in those receiving polymeric encapsulating agents. There is also concern that residual polymer components remain in the tissue well beyond drug delivery [4].

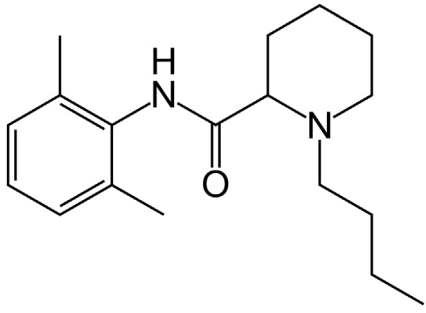

Fig. 1. Chemical structure of bupivacaine. Image provided courtesy of Pacira Pharmaceuticals, Inc [8].

Overview of bupivacaine

Bupivacaine is classified as an amide [-NH-CO-] local anesthetic because the amino or piperidine ring and aromatic ring are linked by an amide group. The chemical structure is shown in Fig. 1. Compared to early local anesthetics that contain an ester [-O-CO-] group, amide compounds are less allergenic and have a longer shelf-life. The potency of bupivacaine is determined by the presence of a lipid-soluble aromatic ring with hydrocarbon groups, while the duration of action is prolonged, as it is 95% protein-bound. Bupivacaine is a racemic mixture of R- and S- enantiomers, with different affinities for sodium, potassium, and calcium ion channels. Potentiation of the S- enantiomer, as seen with ropivacaine and levobupivacaine, is attributed to a reduced risk of cardiovascular and central nervous system toxicity because it has a lower affinity for sodium channels [1–3].

Pharmacokinetics

Systemic absorption of liposomal bupivacaine is dependent on the dose, route of administration, and vascularity of the injection site. Bupivacaine is widely distributed to highly perfused organs such as the heart, brain, lung, liver, and kidneys. The onset of action of bupivacaine HCl is rapid and dependent on the site of administration with an anesthetic effect that can last up to 8 h. Alternatively, liposome encapsulation allows for rapid release of bupivacaine. Specifically, bimodal peaks in concentration have been reported, with initial peaks occurring 1–8 h after drug administration and the second peak occurring 12–36 h later. Given the nonconcentric matrix of the MVL liposomes, degradation of the lipid bilayers with concomitant internal drug redistribution allows delayed release of drug from the aqueous core. Thus, liposome encapsulation extends the duration of therapy to up to 96–120 h.

Bupivacaine is hepatically metabolized by glucuronide conjugation and N-dealkylation into an inactive metabolite, pipecolylxylidine. As mentioned previously, it is approximately 95% protein-bound, thus limiting drug clearance from either hepatic blood flow or hepatic extraction. Data suggest that prolonged exposure to bupivacaine in patients with intrinsic hepatic disease may necessitate dose reduction relative to the degree of dysfunction [5]. A small percentage of bupivacaine is also excreted unchanged in the urine. While dose adjustments are presently not advised for patients with renal dysfunction, reduced clearance and drug accumulation can increase the potential risk of adverse effects [2].

Comparative pharmacokinetics of bupivacaine versus liposomal bupivacaine after a single injection have been studied in both healthy volunteers and surgical patients (e.g., inguinal hernia repair, total knee arthroplasty, hemorrhoidectomy, or bunionectomy) [5,6]. In the study involving healthy adults, participants were randomized to receive 89 mg, 155 mg, or 266 mg of liposomal bupivacaine or 50 mg of bupivacaine HCl (13.3 mg of bupivacaine base is equivalent to 15 mg of bupivacaine HCl). The study revealed that all three doses of liposomal bupivacaine yielded a statistically larger area under the curve (AUC) than bupivacaine HCl (4151-13,954 ng/mL versus 1961 ng/mL, respectively; $p < 0.001$). The maximum concentration (C_{max}) of liposomal bupivacaine 89 mg and 155 mg was significantly lower (120 and 134 ng/mL, respectively) than that of bupivacaine HCl (300 ng/mL; $p < 0.001$), while the C_{max} for the 266 mg dose was slightly lower (250 ng/mL) albeit not statistically significant. The time to maximum concentration (T_{max}) increased 10-fold in the liposomal group (7–24 h) compared to that in the bupivacaine group (0.7 h) [5]. Similarly, Hu et al. also compared the pharmacokinetic parameters of liposomal bupivacaine to bupivacaine HCl 100 mg, bupivacaine HCl 150 mg with epinephrine 1:200,000, or placebo after administration in 4 distinct surgical populations. After a single injection in patients undergoing inguinal hernia repair of either liposomal bupivacaine at doses ranging from 155 mg to 310 mg or bupivacaine HCl 100 mg, there was a dose-proportional increase in both area under the curve AUC_{∞} (9597–19,476 ng/mL versus 4374 ng/mL, respectively) and C_{max} (241–415 ng/mL versus 336 ng/ml, respectively). The T_{max} increased greater than 10-fold, with liposomal bupivacaine ranging 10–12 h. The bupivacaine HCl group had a median T_{max} of 0.6 h. Comparatively, in patients undergoing total knee arthroplasty, liposomal bupivacaine provided greater plasma exposure than bupivacaine HCl as evidenced by an AUC ranging from 7826 to 60,174, with doses of 133–532 mg versus 7460 ng/mL with bupivacaine HCl 150 mg. The C_{max} for all doses of liposomal bupivacaine was higher than that of bupivacaine 150 mg with epinephrine (262–935 ng/ml versus 205 ng/ml,

respectively). This latter finding can be explained by the use of epinephrine with bupivacaine, which is meant to reduce absorption and subsequently affect peak concentrations. Of note, both AUC and C_{max} were exponentially higher with liposomal doses of 532 mg, which is double the Food and Drug Administration (FDA)-approved dose of less than 266 mg. The placebo arms of this study (i.e., the hemorrhoidectomy and bunionectomy populations) are outside the focus of this review and thus will not be discussed [6].

Liposomal bupivacaine can elicit an anesthetic effect lasting for up to 96 h after a single injection. A 2017 study evaluated the pharmacokinetic impact of multiple doses of liposomal bupivacaine in healthy adults [7]. Cohorts received 266 mg of liposomal bupivacaine as either a single injection or a repeated dose with the second injection administered either immediately or up to 72 h after the initial dose. The mean AUC_{last} increased exponentially (3-fold to >10-fold) after the second injection of liposomal bupivacaine. As anticipated, the mean concentration also increased after the second injection of local anesthetic, with a peak C_{max} as high as 589 ng/mL. Similar to the study by Hu et al., which reported a C_{max} of 935 ng/ml, the concentrations after a repeated dose of liposomal bupivacaine within a 72-h period were well below the documented threshold for toxicity of 2000 ng/mL for neurotoxicity and 4000 ng/mL for cardiotoxicity [7].

Pharmacodynamics

Bupivacaine is an amide local anesthetic designed to prevent the conduction of nerve impulse through inhibition of voltage-gated sodium ion channels. The anesthetic effect of bupivacaine on both motor and sensory nerve blockade from the time of single injection until 96 h post dose or functional recovery has been assessed. In the study of healthy volunteers by Viscusi et al., motor blockade of both lower extremities was evaluated using the modified Bromage scale [4]. Reports of motor blockade were highest in patients receiving 266 mg of liposomal bupivacaine and those who received bupivacaine HCl (57% and 100%, respectively). The median time to ambulate freely was similar between the three groups that reported any incidence of motor blockade within the initial 96 h. The onset to sensory block was equivalent in all 3 liposomal bupivacaine groups and the bupivacaine HCl group. Both the duration and time to recovery from numbness to pinprick and cold were significantly prolonged by at least 3-fold following administration of high-dose liposomal bupivacaine (266 mg) when compared to bupivacaine HCl [5]. In general, single or repeated doses of liposomal bupivacaine were well tolerated. The most common adverse events were gastrointestinal upset, pyrexia, headache, and pain at the injection site. These adverse events were considered mild or moderate in severity, and no subject discontinued participation in any study secondary to drug intolerance [5–7].

Surgical considerations

Liposomal bupivacaine in its current formulation is available in vials of 10 and 20 ml with a 13.3 mg/mL formulation for a total of 133 mg and 266 mg per vial, respectively [8]. Currently, the maximum dose per the manufacturer is 266 mg or 20 ml. However, the total dose used needs to take into consideration other factors such as patient comorbidities, size of the surgical site, and volume needed to cover the affected area. Importantly, if used at a peripheral nerve site, the total dose is halved to 133 mg to avoid local anesthetic toxicity [8].

Liposomal bupivacaine can be used in its undiluted state providing practitioners with 20 mL of volume for infiltration. If dilution is needed, clinicians can add normal saline or lactated ringers to dilute the initial concentration resulting in a 0.89 mg/mL solution. Diluted formulations allow clinicians to disperse more volume over larger spaces. Of note, hypotonic solutions should be avoided for fear of disrupting the liposomal complex [8]. Interestingly, some practitioners choose to dilute liposomal bupivacaine with other local anesthetics. It is important to note that this practice is not currently approved by the FDA. If bupivacaine HCl is used, clinicians need to be aware that the effects of bupivacaine HCl and liposomal bupivacaine are additive and need to monitor patients closely for signs of local anesthetic toxicity. When combined, it is important that the ratio of bupivacaine HCl to liposomal bupivacaine does not exceed 1:2. Co-administration of nonbupivacaine local anesthetics should be

avoided due to the high likelihood of disassociating the liposomal complex, which could result in immediate release [8].

Current evidence supports liposomal bupivacaine use for infiltration into surgical sites to help decrease postsurgical incisional pain by transverse abdominis plane (TAP) and interscalene brachial plexus nerve blocks (ISB) [1,8]. A comprehensive list of FDA-approved and nonapproved applications is given in Table 1. Because of its relatively similar safety profile to bupivacaine HCl, liposomal use for off-label applications has accelerated with interest in broader applications for peripheral nerve blocks. While there are published case reports and small trials documenting the utility of liposomal bupivacaine for other indications, practitioners need to be extremely cautious when used for off-label uses related to the lack of validation. We recommend that liposomal bupivacaine be used only for FDA-approved indications until future studies are completed that validated broader indications [8,9].

While many clinicians consider TAP blocks a regional anesthesia technique, the FDA classifies TAP blocks as local infiltration. Numerous studies have demonstrated the efficacy of liposomal bupivacaine in TAP blocks to decrease postsurgical pain and opiate consumption when compared to bupivacaine HCl [10]. It is important to note that TAP block efficacy is predicated primarily on volume and spread across the transverse abdominis plane. Because of this, most practitioners will opt to dilute the standard solution to achieve appropriate spread bilaterally [9].

Despite a favorable analgesic profile and potential future indications, liposomal bupivacaine is currently not indicated for use in the obstetric population. One of the major limitations to surgical site infiltration is that bupivacaine HCl used for paracervical blocks has been associated with fetal bradycardia and death [11]. The pathophysiology is thought to be related to its ability to readily disassociate across the placental barrier and then be trapped in fetal circulation, subsequently resulting in toxicity [12,13]. Of note, there is an early phase clinical trial currently underway looking at liposomal bupivacaine infiltration after cesarean section that is due to conclude in 2020. However, until more evidence supports its use in patients less than 18 years of age or those who are gravid, we do not recommend use unless part of an informed, formal investigational study.

Future local anesthetics

There are also several novel local anesthetic pharmacotherapies that are currently undergoing early phase clinical trials. SABER-bupivacaine is another depot formulation used for surgical infiltration that allows for the sustained release of bupivacaine [14]. This formulation encapsulates bupivacaine in a biodegradable sucrose acetate isobutyrate biolayer [14–16]. Very limited clinical data are currently available to assess the safety and efficacy of another bupivacaine formulation with extended release. To date, there has been only one published randomized controlled trial investigating the use of SABER-bupivacaine wound infiltration. The double-blind RCT included 124 patients undergoing inguinal hernia repair and compared pain scores and opioid use between SABER-bupivacaine and SABER-placebo. Findings were significant for decreased pain and opioid use in the SABER-bupivacaine group compared to that in the placebo group. While data are promising, much more data are needed before validation.

HTX-011 is an investigational extended-release local anesthetic formulation currently undergoing Phase 3 clinical trials [14]. HTX-011 was developed by Heron Therapeutics and is composed of a bioerodible polymer with bupivacaine and low-dose meloxicam [14]. Meloxicam is posited with bupivacaine to help potentiate bupivacaine analgesia. The polymer undergoes hydrolysis and allows for

Table 1
Approved versus nonapproved off-label use of liposomal bupivacaine.

FDA-Approved Uses	Non-FDA-Approved Uses
Hemorrhoidectomy	Peripheral Nerve Blocks
Bunionectomy	Intercostal Nerve Blocks
Transversus Abdominis Plane Block	Epidural Injection
Mammoplasty: Local Infiltration	Total Knee Arthroplasty: Intra-articular
Total Knee Arthroplasty: Local Infiltration	
Inguinal Hernia Repair: Local Infiltration	

sustained release of bupivacaine and meloxicam for 3 days. HTX-011 has been studied in small populations of patients undergoing bunionectomy and inguinal hernia repair with promising results thus far. Both populations were noted to have lower pain scores at 72 h with a significant reduction in opioid consumption when compared to bupivacaine HCl and placebo [14]. No research has yet been conducted to evaluate its potential role in peripheral nerve blocks. Microspheres and nanoparticles were discussed in detail earlier in this paper. While still in their infancy, these novel medication delivery mechanisms also have the potential to significantly improve drug delivery and perioperative pain control.

Conclusion

As implementation of regional anesthetic techniques continues to grow and become standard of care, clinicians need to be cognizant of the pharmacological and physiological properties of the medications used. Liposomal bupivacaine has proven to have a significant benefit on patient satisfaction, outcomes, and safety in the perioperative setting. The development of novel extended-release local anesthetic formulations will likely play a major role for opioid-sparing techniques in the future. While FDA-approved indications are currently relatively limited, these will no doubt expand in the coming years as larger studies are performed and more evidence is ascertained.

Practice points

- Novel preparations allowing extended duration of action of local anesthetics have many clinically relevant benefits.
- Additive and/or synergistic effects between medications can help decrease the total amount of medication given and therefore help limit adverse effects such as respiratory depression and toxicity.
- Liposomal bupivacaine allows for a slow and sustained release of local anesthetic at the intended site of action without the need for a perineural catheter.
- The unique liposomal bilayer that encapsulates bupivacaine allows for a sustained release of local anesthetic for up to 72 h after a single use and can significantly decrease postoperative opioid consumption.

Research agenda

- We recommend that liposomal bupivacaine be used for only FDA-approved indications until future studies are completed that validate broader indications.
- Despite a favorable analgesic profile and potential future indications, liposomal bupivacaine is currently not indicated for use in the obstetric population. Additional research within this population is necessary before it can be used.
- SABER-bupivacaine is another depot formulation used for surgical infiltration that allows for the sustained release of bupivacaine. While data are promising, much more data are needed before validation.
- HTX-011 is an investigational extended-release local anesthetic formulation currently undergoing Phase 3 clinical trials. No research has yet been done to evaluate its potential role in peripheral nerve blocks.

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